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Evaluation of patient demographics, clinical characteristics, and cardiovascular outcomes in patients with type 2 diabetes newly initiated on sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and other antidiabetic medications

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Evaluation of patient demographics, clinical characteristics, and cardiovascular outcomes in patients with type 2 diabetes newly initiated on sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and other antidiabetic medications

by

Elmor David Pineda

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Dedication

This thesis is dedicated to my loving and caring family and friends for their unwavering support in my journey of lifelong learning. To my parents, both of whom have made continued sacrifices throughout my life in my pursuit of happiness and success: thank you for everything that you have given me.

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Abstract

Evaluation of patient demographics, clinical characteristics, and cardiovascular outcomes in patients with type 2 diabetes newly initiated on sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and other antidiabetic medications

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The University of Texas at Austin, 2019

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Objectives: To evaluate and compare patient characteristics and cardiovascular outcomes among adults with type 2 diabetes (T2D) newly initiated on sodium-glucose cotransporter-2 inhibitors (SGLT-2is), glucagon-like peptide-1 receptor agonists (GLP-1RAs), and other antidiabetic medications (oADMs).

Methods: This retrospective new user cohort study used administrative claims and electronic health record data from an integrated delivery network in Texas. Patients ages ≥18 years with T2D and ≥1 prescription claim for either a SGLT-2i, GLP-1RA, or oADM filled between April 2013 through December 2018 were included. Patients were divided into three 1:1 propensity matched groups according to index medication identified. Pairwise comparisons of patient characteristics between SGLT-2is versus oADMs, GLP-1RAs versus oADMs, and SGLT-2is versus GLP-1RAs were compared before and after matching. Primary outcomes were heart failure hospitalization and a composite endpoint

of myocardial infarction, stroke, unstable angina, or coronary. Secondary outcomes were the individual components of the composite endpoint. Cumulative incidences of all outcome variables were described using Kaplan-Meier failure plots and compared using log-rank tests and cox regression models.

Results: Among 9,477 patients, 1,134 were SGL-2is initiators, 1,072 were GLP-1RA initiators, and 7,271 were oADM initiators. After propensity score matching, there were 815 matched pairs for SGLT-2i versus oADM), 817 pairs for GLP-RA versus oADM, and 947 pairs for SGLT-2i versus GLP-1RA. Patients initiating SGLT-2is versus oADMs had significantly lower risk of the composite endpoint (HR 0.69, 95% CI: 0.52-0.92), heart failure hospitalization (HR 0.66, 95% CI: 0.47-0.93), and unstable angina requiring hospitalization (HR 0.58, 95% CI: 0.41-0.82). Patients initiating SGLT-2is compared to oADMs had significantly lower risk of the composite endpoint (HR 0.70, 95% CI: 0.52-0.94) and unstable angina requiring hospitalization (HR 0.59, 95% CI: 0.42-0.83). There were no differences in CV outcomes between SGLT-2is and GLP-1RAs.

Conclusions: Both SGLT-2is and GLP-1RAs showed significant reductions in the composite outcome and unstable angina requiring hospitalization versus oADMs. However, only SGLT-2is were associated with a lower risk for heart failure hospitalizations. Nevertheless, CV outcomes were similar between SGLT-2is and GLP-1RAs when compared to each other. This study provides real-world evidence for patients, payers, and providers, to consider selection of novel antidiabetic agents with CV benefits, SGLT-2is and GLP-1RAs, over other agents regardless of CVD status.

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Chapter 1: Introduction

1.1 Epidemiology of Type 2 Diabetes

Type 2 Diabetes (T2D) is a complex metabolic disorder that is characterized by persistent hyperglycemia as a result of varying degrees of insulin resistance and impaired insulin secretion.[1] Rates of both prevalence and incidence have been steadily increasing, mainly due to increases in obesity, sedentary lifestyles, and an increasing minority population. The Centers for Disease Control and Prevention's (CDC) 2017 National Diabetes Statistics Report estimates that a total of 30.3 million adults ages 18 years or older in the United States (US), 9.4% of the population, have diabetes with an incidence rate of approximately 1.5 million new cases of diabetes each year.[2] The Southern and Appalachian regions of the US tend to have the highest prevalence rates of diabetes compared to others. In Texas, the estimated age-adjusted prevalence among adults was 10.9% (about 2.3 million) where Wichita, Tarrant, Waller, Angelina, Nacogdoches, Bowie, Anderson, and Dallas are among the top counties with the highest rates of prevalence.[3] While these estimates do not differentiate between Type 1 Diabetes (T1D), T2D, and other diabetes types, they are more representative of the T2D population since it accounts for a disproportionately greater contribution to the prevalence of diabetes, representing 90-95% of all diabetes cases.[1,2]

An analysis conducted using data from the National Health Interview Survey from 2016 found that 8.6% of the US population (21.0 million) had T2D, while 0.55% (1.3 million) had T1D and 0.31% (0.8 million) had other diabetes types.[4] The age group with the highest prevalence is ≥65 years (19.62%) followed by 45-64 (11.03%), 30-44 (3.29%), and 18-29 (0.66%), which shows an increase in prevalence with age. Although prevalence is similar for males and females, it varies between racial and ethnic groups where it is highest in non-Hispanic blacks (11.52%) followed by Hispanics (9.07%), Asians (6.89%), and non-Hispanic whites (7.99%).

1.2 PATHOPHYSIOLOGY OF TYPE 2 DIABETES

Patients with T2D exhibit defects in normal glucose metabolism, including impaired insulin secretion, insulin resistance, excess glucagon secretion, and glucagon-like-peptide-1 (GLP-1) deficiency and resistance.[1] Normally, insulin and glucagon work together to maintain normal plasma glucose levels in both the fasting and postprandial state. Insulin is released from pancreatic β-cells to lower plasma glucose levels by promoting glucose uptake and storage, while pancreatic α-cells release glucagon to counteract insulin's effects by stimulating gluconeogenesis and glycogenolysis. Defects in one or both mechanisms can lead to clinically significant dysregulation of plasma glucose levels.

Pancreatic β-cells rely on feedback regulation from insulin-sensitive tissues, including skeletal muscle tissue, adipose tissue, and liver tissue, in order to regulate their insulin secretion. Similarly, insulin-sensitive tissues rely on feedback from β-cells in the form of insulin secretion to mediate their uptake of glucose, fatty acids, and amino acids. During the early stages of insulin resistance, β-cells have the ability to increase insulin secretion through compensatory hyperinsulinemia and maintain glucose levels within normal physiological range.[1,5,6] However, β-cells are only capable of increasing insulin output to a certain extent in order to compensate for worsening insulin resistance. Over time, the demand for insulin overcomes the supply, which results in elevations in plasma glucose. This inability to meet insulin demand to overcome peripheral insulin resistance is further compounded by progressive β-cell dysfunction or impaired insulin secretion, ultimately, leading to persistent hyperglycemia.

The incretin system also plays an important role in maintaining normal plasma glucose homeostasis.[1] Incretin hormones, GLP-1 and glucagon-dependent insulinotropic polypeptide (GIP), are released from intestinal endocrine cells in the small intestinal mucosa to stimulate insulin secretion in response to a meal.[1,7,8] Both GLP-1 and GIP are the two principal mediators of the incretin effect that is responsible for a substantial portion of the postprandial insulin secretory response. The incretin effect refers to the 73% higher difference in insulin release that is observed

in a patient without T2D after an oral glucose load compared to an equivalent intravenous load in the same subject. This incretin effect is reduced or absent in the presence of impaired glucose tolerance and T2D, suggesting its role in the pathogenesis in T2D.

The insulinotropic effects of GLP-1 remain relatively preserved compared to those of GIP in T2D. Experiments assessing the dose-response relationship between GLP or GIP and insulin secretion in patients with T2D demonstrated that supratherapeutic infusions of GIP had little to no effect on insulin secretion in response to glucose infusions, whereas similar infusions of GLP-1 had significant effects on insulin secretion and normalized β-cell sensitivity and responsiveness to glucose.[7–9] However in subsequent experiments, infusions resulting in normal physiological concentrations of GLP-1 or GIP failed to show similar responsiveness, suggesting diminished GLP-1 potency in T2D.[7,9]

1.3 CARDIOVASCULAR DISEASE IN TYPE 2 DIABETES

Cardiovascular disease (CVD) is the most prevalent cause of morbidity and mortality in patients with T2D.[10] Patients with T2D have a disproportionately two-four-fold higher risk for atherosclerotic disease and develop CVD approximately 15 years earlier than their nondiabetic counterparts.[11,12] It is estimated that approximately 32.2% of all patients with T2D have CVD, and roughly two-thirds of deaths in this population are CVD related.[10] A majority of this excess risk can be attributed to the high prevalence of additional underlying risk factors that are widely present in this population, which includes hypertension, dyslipidemia, obesity, sedentary lifestyle, chronic kidney disease (CKD), and smoking. Thus, the link between T2D and CVD is multi-factorial and control of blood glucose alone does not necessarily eliminate CV risk.[10,12] Joint management of T2D and CVD is imperative in lowering risk of CV events, including myocardial infarction (MI), coronary heart disease, ischemic stroke, and heart failure.

Multiple mechanisms exist that participate in driving an increased risk for atherosclerotic CVD (ASCVD) in T2D, creating the perfect environment for atherosclerosis to occur.[10] It has been

estimated that for every 1% increase in hemoglobin A1c (HbA1c) there is a 12% to 16% increase in CV events.[13] Hyperglycemia, insulin-resistance, and hyperinsulinemia, promote an increase in inflammation, oxidative stress, and a reduction in nitric oxide bioavailability, leading to endothelial dysfunction and greater atherosclerotic plaque burden.[14–16] Inflammation promotes atherosclerotic lesions and increases the risk for hypercoagulability due to elevated circulating tissue factor, procoagulant proteins, and increased concentrations of plasminogen activator inhibitor-1 antigens. Patients with T2D also have higher rates of hypertension, dyslipidemia, obesity, and impaired glucose tolerance, which contributes to the development and progression of atherosclerosis as well. In the setting of compensatory hyperinsulinemia, endothelial dysfunction is further increased due to an increase in vasoconstrictors. In addition, atherosclerotic plaques tend to be more unstable in patients with T2D, which can lead to plaque rupture and thrombosis.

1.4 ECONOMIC BURDEN

According to an economic report released by the American Diabetes Association (ADA) in 2018, the estimated total costs of diagnosed diabetes in the US in 2017 was $327 billion, which includes $237 billion in direct medical costs and $90 billion in lost productivity.[17] This represented a 26% increase in total costs from $245 billion in 2012 and is expected to increase due to growths in both prevalence and medical costs.[17,18] The largest drivers of direct medical costs were higher utilization of prescription medications to treat comorbid conditions of diabetes ($71.2 billion; 30%) and hospital inpatient care ($69.7 billion; 30%), followed by antidiabetic medications and diabetes supplies (34.6 billion; 15%) and physician office visits ($30.0 billion; 13%).[17] In addition to its significant clinical burden in diabetes, CVD has been identified as one of the primary cost drivers for medical costs for diabetes comorbidities and accounts for a quarter to one-half of all direct costs for diabetes.[17–19] Adults with CVD and diabetes incur an additional $3,400 to $9,700 per patient per year in health care costs compared to adults with only diabetes.[19] It was estimated

that in 2017, $37.3 billion in cardiovascular-related spending was associated with diabetes in the US alone.[17]

1.5 CARDIOVASCULAR OUTCOME TRIALS

In 2008, the Food and Drug Administration (FDA) issued a Guidance for Industry stating that all new pharmacological treatments for T2D should rule out unacceptable cardiovascular risk consisting of at least a three-point major adverse cardiovascular event (3P-MACE) composite of CV death, nonfatal MI, and nonfatal stroke.[20] The upper limit of the 95% confidence interval for the hazard ratio had to be <1.8 for pre-marketing studies and <1.3 for post-marketing studies. The FDA's guidance on establishing CV safety for novel antidiabetic medications were a result of the high CVD prevalence and burden in the T2D population coupled with the potential harm in increased CV risk that was found to be associated with traditional diabetes medications, such as the thiazolidinedione (TZD), rosiglitazone,[21] and the dual peroxisome proliferator-activated receptor-α and -γ agonist, muraglitazar.[22] These safety trials were meant to be designed as noninferiority trials to demonstrate that new antidiabetic agents are not associated with more major adverse cardiovascular events (MACE) compared to placebo; however, some of these trials were also powered to assess superiority as well to establish CV benefit. Prior to the FDA's guidance statement, antidiabetic agents were largely evaluated upon their ability to lower glucose levels with the idea that improving glycemic control would benefit microvascular outcomes (retinopathy, neuropathy, and nephropathy). However, there was less certainty regarding whether there were CV benefits with intensive glycemic control due to negative findings from landmark trials, UKPDS, ACCORD, ADVANCE, and VADT, which showed no significant reductions in macrovascular outcomes.[23–26]

As a result of several cardiovascular outcome trials (CVOTs) following the FDA Guidance statement, antidiabetic medications within two therapeutic drug classes, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT-2is)

provided positive results showing significant reductions in the risk of CV events in T2D patients, suggesting their cardioprotective effects. Currently, only three antidiabetic drugs have received FDA-approved labeling for CV risk reduction in patients with T2D and established CVD. Empagliflozin was the first antidiabetic agent to receive FDA-approval for CV risk reduction in 2016, specifically to reduce the risk of CV mortality in adults with T2D and established CVD. Then in 2017, liraglutide became the first antidiabetic agent to receive FDA-approved labeling to reduce the risk of MACE (CV death, nonfatal MI, and nonfatal stroke) in adults with T2D and established CVD. Canagliflozin is the latest antidiabetic agent to receive approval for MACE risk reduction, which it gained in 2018. Most recently, the manufacturer of semaglutide filed for FDA-approval for the same indication in March 2019.

1.6 GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

GLP-1RAs are a class of antidiabetic medications that are indicated for the treatment of T2D. They work to lower plasma glucose concentrations through multiple mechanisms by mimicking endogenous GLP-1 activity through activation of their receptors. This results in increased glucose-dependent insulin secretion, decreased inappropriate glucagon secretion, increased β-cell growth/replication, slowed gastric emptying, and decreased food intake. There are currently five out of six FDA-approved GLP-1RAs on the market: dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide. The sixth, albiglutide, was removed from the market by its manufacturers who announced their decision to discontinue the product in August 2017 and stated that it would no longer be available as of May 2018 due to a lack of utilization.

The results of 5 CVOTs, ELIXA (lixisenatide),[27] LEADER (liraglutide),[28] SUSTAIN-6 (semaglutide),[29] EXSCEL (exenatide),[30] and HARMONY OUTCOMES (albiglutide)[31] have been published. The results from a sixth trial, REWIND (dulaglutide) have not yet been published; however, findings announced from an initial press release have shown significant reductions in 3P-MACE compared to placebo.[32] Results for each trial are summarized in Table 1.6.1.

Table 1.6.1 Summary of cardiovascular outcomes trials for glucagon-like peptide-1 receptor agonists

	ELIXA[27]	**LEADER**[28]	**SUSTAIN-6**[29]	**EXSCEL**[30]	**HARMONY OUTCOMES**[31]
Author (year)	Pfeffer et al. (2015)	Marso et al. (2016)	Marso et al. (2016)	Holman et al. (2017)	Hernandez et al. (2018)
Sample Size (patients)	6,068	9,340	3,297	14,752	9,463
Drug	Lixisenatide vs. placebo	Liraglutide vs. placebo	Semaglutide vs. placebo	Exenatide once weekly vs. placebo	Albiglutide once weekly vs. placebo
Main inclusion criteria	T2D with acute coronary event within 180 days prior to screening	T2D with pre-existing CVD, HF, or CKD ≥50 years of age or 1 CV risk factor ≥60 years of age	T2D with pre-existing CVD, HF, or CKD ≥50 years of age or 1 CV risk factor ≥60 years of age	T2D with or without pre-existing CVD	T2D with CVD ≥40 years of age
HbA1c (%)	5.5-11.0	≥7.0	≥7.0	6.5-10.0	>7.0
Mean Age (years)	60.3	64.3	64.6	62	64.1
Median Follow-Up (years)	2.1	3.8	2.1	3.2	1.6
Primary Outcome	4P-MACE*	3P-MACE†	3P-MACE†	3P-MACE†	3P-MACE†
	HR 1.02, CI (0.89-1.17)	HR 0.87, CI (0.78-0.97)	HR 0.74, (0.58-0.95)	HR 0.91, CI (0.83-1.00)	HR 0.78, CI (0.68-0.90)
	P=0.81 for superiority P<0.001 for noninferiority	P=0.01 for superiority P<0.001 for noninferiority	P=0.02 for superiority P<0.001 for noninferiority	P=0.06 for superiority P<0.001 for noninferiority	P=0.0006 for superiority P<0.0001 for noninferiority
Secondary Outcomes					
Expanded MACE‡	HR 1.00, CI (0.90-1.11)	HR 0.88, CI (0.81–0.96)	HR 0.88, CI (0.62–0.89)	-	-
4P-MACE*	-	-	-	-	HR 0.78, CI (0.69–0.90)
MI	HR 1.03, CI (0.87–1.22)	HR 0.86, CI (0.73–1.00)	HR 0.74, CI (0.51–1.08)	HR 0.97, CI (0.85–1.10)	HR 0.75, CI (0.61–0.90)
Stroke	HR 1.12, CI (0.79–1.58)	HR 0.86, CI (0.71–1.06)	HR 0.61, CI (0.38–0.99)	HR 0.85, CI (0.70–1.03)	HR 0.86, CI (0.66–1.14)
CV Death	HR 0.98, CI (0.78–1.22)	HR 0.78, CI (0.66–0.93)	HR 0.98, CI (0.65–1.48)	HR 0.88, CI (0.76–1.02)	HR 0.93, CI (0.73–1.19)
Unstable Angina	HR 1.11, CI (0.47–2.62)	HR 0.98, CI (0.76–1.26)	HR 0.82, CI (0.47–1.44)	HR 1.05, CI (0.94–1.18)	-
HF Hospitalization	HR 0.96, CI (0.75–1.23)	HR 0.87, CI (0.73–1.05)	HR 1.11, CI (0.77–1.61)	HR 0.94, CI (0.78–1.13)	-

***** Composite endpoint including nonfatal MI, nonfatal stroke, and CV death, and unstable angina

† Composite endpoint including nonfatal MI, nonfatal stroke, CV death

‡ Composite endpoint including nonfatal MI, nonfatal stroke, CV death, unstable angina, and HF hospitalization

HbA1c = Hemoglobin A1c; CI = 95% Confidence interval; CV = Cardiovascular; CVD = Cardiovascular disease; HF = Heart failure; HR = Hazard ratio; MACE = Major adverse cardiovascular events; MI = Myocardial infarction; T2D = Type 2 diabetes

ELIXA, LEADER, SUSTAIN-6, and HARMONY OUTCOMES were carried out in patient populations with either established CVD or very high CV risk as well as T2D.[27–29,31] On the other hand, EXSCEL was conducted in those with T2D regardless of the presence of prior CVD with 73.1% having established CVD.[30] All GLP-1RAs did not show an increase in CV events compared with placebo.[27–29,31] Moreover, liraglutide, semaglutide, and albiglutide significantly decreased the risk of primary composite endpoint of cardiovascular events by 13%, 26%, and 22% (HR 0.87, 95% CI: 0.78-0.97, HR 0.74, 95% CI: 0.58-0.95, and HR 0.78, 95% CI: 0.68-0.90) compared with placebo, respectively.[28,29,31] In contrast, lixisenatide and exenatide did not show a statistically significant reduction in the risk.[27,30] Thus, the results of the association between the use of GLP-1RAs and CV risks may vary among the agents. However, the lack of significant CV risk reduction observed in ELIXA and EXSCEL may be related to multiple factors such as differences in the median follow-up time, the duration of exposure to the trial regimen, inclusion of patients with recent acute coronary syndrome who have a higher CV event risk, and the rate of discontinuation of the trial regimen due to adverse events. In addition, structural and pharmacokinetic differences may help to explain the varying clinical effects. However, specific reasons as to why the association between the use of GLP-1RAs and CV risks may vary among the agents, as well as the underlying mechanisms of the difference have not yet been explained.

Several mechanisms have been proposed to explain the underlying CV benefits of GLP-1RAs. The associated favorable weight loss to address obesity as a CV risk factor is due to their ability to decrease the rate of gastric emptying, thereby suppressing appetite. In addition to beneficial weight loss effects, they have been shown to reduce blood pressure, inflammation, ischemic injury, smooth muscle proliferation, and platelet aggregation, as well as increase vasodilation, blood flow, natriuresis, left ventricular function and heart rate, endothelial function, and plaque stability.[33] Additionally, GLP-1RAs have demonstrated favorable effects on lipid levels by reducing total cholesterol, low-density lipoprotein, triglycerides, and apolipoprotein B.

1.7 SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS

SGLT-2is are the latest class of antidiabetic agents to receive FDA approval that are indicated for the treatment of T2D. They exert their insulin-independent antihyperglycemic effects by inhibiting SGLT-2 in the proximal renal tubules of the nephrons, where roughly 90% of urinary glucose reabsorption occurs, to reduce reabsorption of filtered glucose from the tubular lumen and to lower the renal threshold for glucose, thereby increasing the urinary excretion of filtered glucose.[34–36] There are currently four FDA approved SGLT-2is: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. Canagliflozin, approved in April 1, 2013, was the first SGLT-2i marketed in the US.

The results of 3 CVOTs, EMPA-REG OUTCOME (empagliflozin),[37] CANVAS (canagliflozin),[38] and DECLARE-TIMI 58 (dapagliflozin),[39] have been published. A 4th trial, VERTIS-CV (ertugliflozin), has not yet been completed. Results from each trial are summarized in Table 1.7.1.

Table 1.7.1 Summary of cardiovascular outcome trials for sodium-glucose cotransporter-2 inhibitors

	EMPA-REG OUTCOME[37]	**CANVAS**[38]	**DECLARE-TIMI 58**[39]
Author (year)	Zinman et al. (2015)	Neal et al. (2017)	Wiviott et al. (2018)
Sample Size (patients)	7,020	10,142	17,160
Drug	Empagliflozin vs. placebo	Canagliflozin vs. placebo	Dapagliflozin vs. placebo
Main inclusion criteria	T2D with pre-existing CVD with BMI ≤ 45 kg/m^2 and eGFR ≥ 30 mL/min/1.73 m^2	T2D with pre-existing CVD ≥30 years of age or ≥2 CV risk factors ≥50 years of age	T2D with pre-existing CVD ≥40 years of age or CV risk factors ≥55 years of age (men) ≥60 years of age (women) and CrCl ≥ 60 mL/min
HbA1c (%)	7.0-10.0	7.0-10.5	≥6.5-12.0
Mean Age (years)	63.1	63.3	64.0
Median Follow-Up (years)	3.1	2.4	4.2
Primary Outcome	3P-MACE*	3P-MACE*	3P-MACE*
	HR 0.86, CI (0.74–0.99)	HR 0.86, CI (0.75–0.97)	HR 0.93, CI (0.84–1.03)
	P=0.04 for superiority P<0.001 for noninferiority	P=0.02 for superiority P<0.001 for noninferiority	P=0.17 for superiority P<0.001 for noninferiority
			CV death or HF Hospitalization
			HR 0.83, CI (0.73–0.95)
			P=0.005 for superiority
Secondary Outcomes			
4P-MACE*	HR 0.89, CI (0.78–1.01)	-	-
MI	HR 0.87, CI (0.70–1.09)	HR 0.89, CI (0.73–1.09)	HR 0.89, CI (0.77–1.01)
Stroke	HR 1.18, CI (0.89–1.56)	HR 0.87, CI (0.69–1.09)	HR 1.01, CI (0.84–1.21)
CV Death	HR 0.62, CI (0.49–0.77)	HR 0.96, CI (0.77–1.18)	HR 0.98, CI (0.82–1.17)
Unstable Angina	HR 0.99, CI (0.74–1.34)		
HF Hospitalization	HR 0.65, CI (0.50–0.85)	HR 0.67, CI (0.52–0.87)	HR 0.73, CI (0.61–0.88)

***** Composite endpoint including nonfatal MI, nonfatal stroke, and CV death

CI = 95% Confidence interval; CV = Cardiovascular; CVD = Cardiovascular disease; HbA1c = Hemoglobin A1c; HF = Heart failure; HR = Hazard ratio; MACE = Major adverse cardiovascular events; MI = Myocardial infarction; T2D = Type 2 diabetes

Both EMPA-REG OUTCOME and CANVAS recruited patients with T2D and established CVD, whereas DECLARE-TIMI 58 also considered patients with high CV risk as well with 40.7% of the population having established ASCVD. While empagliflozin and canagliflozin were found to both significantly reduce 3P-MACE by 14% (HR 0.86, 95% CI: 0.74–0.99 and HR 0.86, 95% CI: 0.75–0.97, respectively) compared to placebo, dapagliflozin was only neutral in regards to 3P-MACE. However, dapagliflozin was also powered for superiority to detect differences in the composite of heart failure hospitalizations and CV death and was found to significantly reduce the risk by 17% (HR 0.83, 95% CI: 0.73–0.95) compared to placebo.[39] This was most likely driven by reductions in heart failure hospitalizations since assessment of secondary outcomes revealed a non-significant reduction in CV death (HR 0.98, 95% CI: 0.82–1.17), but a significant reduction in hospitalizations for heart failure (HR 0.73, 95% CI: 0.61–0.88). These positive feart-failure related findings are consistent with empagliflozin and canagliflozin as well (HR 0.65, 95% CI: 0.50–0.85 and HR 0.73, 95% CI: 0.61–0.88, respectively), which may be a signal that this may be a class effect; however, empagliflozin is the only SGLT-2i that showed significant reductions in CV death (HR 0.62, 95% CI: 0.49–0.77). Findings from CVOTs suggest that improvements in CV event risk may be more likely attributable to favorable hemodynamic changes rather than reductions in atherosclerotic burden, since improvements in heart failure hospitalizations occurred early in these trials.

There are several proposed mechanisms to help explain the underlying CV benefits of SGLT-2is, independent of their glucose lowering properties. SGLT-2is have been shown to improve ventricular loading conditions through their diuretic and natriuretic effect, resulting in a reduction in preload.[34] In addition, they have been shown to reduce blood pressure, arterial stiffness, and attenuate cardiac remodeling. They are also associated with improvements in cardiac metabolism and bioenergetics, thereby improving cardiac efficiency and output. This is thought to be mediated by a shift to a more efficient ketone-based cardiac metabolism to support bioenergetic homeostasis. Another proposed mechanism is their ability to decrease uric acid levels, which has

been associated with an increased risk in CV-related events; however, it is debated whether elevated uric acid levels is an independent predictor of CV risk.[40]

1.8 TREATMENT GUIDELINES FOR TYPE 2 DIABETES

While conventional goals of therapy are directed towards achieving optimal blood glucose levels, current recommended approaches to treatment requires continuous medical care utilizing multifactorial risk-reduction strategies that go beyond glycemic control. The primary goal in managing T2D is to reduce the risk of microvascular and macrovascular complications.[41]

T2D management encompasses both lifestyle management and utilization of oral and injectable antihyperglycemic agents.[42–44] The first step in the management of newly diagnosed T2D is to initiate lifestyle management, set an HbA1c target, and then initiate pharmacotherapy based on HbA1c at diagnosis. The ADA recommend an HbA1c goal of <7% for most patients with T2D with consideration for a more stringent goal of <6.5% or less stringent goal of <8% depending on patient specific factors, including hypoglycemia risk, duration of T2D, life expectancy, comorbid conditions, and/or complexity of pharmacotherapy. On the other hand, the American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) support a HbA1c goal of ≤6.5% for most patients or a goal set >6.5% up to 8% if lower targets cannot be achieved without adverse events.[44]

The ADA and AACE/ACE have published comprehensive treatment algorithms and guidelines for T2D management. For those with an initial HbA1c <9%, monotherapy may be considered, while those with an HbA1c >9% should consider dual therapy, and those with HbA1c >10%, high blood glucose (>300 mg/dl), or symptoms of hyperglycemia may consider combination injectable therapy. If HbA1c target is not achieved or maintained within 3 months, or at any point, lifestyle management should be reinforced and dual therapy considered.

The emerging evidence of CV benefit of novel antihyperglycemic agents has created a paradigm shift in the management of T2D from focusing only on glycemic targets to focusing on

CV risk reduction. Consequently, both the ADA and AACE updated their algorithms to incorporate consideration of ASCVD at the point of dual therapy given the results of recently published CVOTs which suggests that certain antihyperglycemic drug classes, namely SGLT-2is and GLP-1RAs, may decrease the rate of CVD events and mortality through mechanisms in addition to their glycemic effects. In patients who do not have ASCVD, they recommend to consider a combination of metformin and any one of the preferred six treatment options: GLP-RA, SGLT-2i, dipeptidyl peptidase-4 inhibitor (DPP-4i), sulfonylurea, TZD, or basal insulin; the choice of which agent to add is based on drug specific effects and patient factors. However, for patients with ASCVD, they recommend adding a second agent with evidence of CV risk reduction after consideration of drug-specific and patient factors. At the time these guidelines were published, liraglutide, empagliflozin, and canagliflozin were the only drugs to receive FDA approved labeling to reduce CV risk in patients with T2D and established CVD. However, the manufacturers of semaglutide have recently submitted for FDA-approval of the same indication as well.

In addition, CVD management in T2D encompasses use of anti-hypertensive agents, lipid-lowering therapy, and anti-platelet therapy to decrease CVD risk in addition to glycemic control. Both the ADA and AACE both recommend a more comprehensive approach to T2D management to include managing CVD risk factors, such as hypertension and dyslipidemia. Others include smoking, family history of premature coronary disease, CKD, and the presence of albuminuria.

1.9 STUDY RATIONALE

The prevalence and economic burden of diabetes is steadily increasing with T2D representing 90-95% of all diabetes cases. CVD remains to be the most prevalent cause of morbidity and mortality in patients with T2D and is a primary cost driver for healthcare costs associated with diabetes management. While lifestyle modifications and metformin are still recommended as initial therapy, new guidelines have been updated by the ADA and AACE/ACE

incorporating recommendations on glucose-lowering medications with CV benefits, as well as emphasizing CV risk management. Antidiabetic agents within the SGLT-2i and GLP-1RA drug classes have demonstrated significant reductions in CV end points in CVOTs compared to placebo. However, it is uncertain whether these findings can be applied to the broader T2D population since these trials specifically included patients with established or high CV risk.

To date, the real-world comparative potential reduction in CV outcomes associated with the use of SGLT-2is and GLP-1RAs compared to other antidiabetic medications (oADMs) as well as the comparative effects between the two classes in routine clinical practice remain uncertain. Although SGLT-2is and GLP-1RAs have shown positive benefits in CV outcomes, there have been no direct comparisons made between SGLT-2is versus GLP-1RAs. In a meta-analysis of 5 GLP-1RA trials and 3 SGLT-2i trials that included 77,242 patients, 42,920 from GLP-1RA trials and 34,322 from SGLT-2i trials, comparing cardiovascular benefits of both drug classes in patients with and without ASCVD, both SGLT-2is and GLP-1RAs showed similar reductions in MACE 11% (HR, 0.89, 95% CI 0.83-0.96; P=0.001) versus 12% (HR, 0.88, 95% CI 0.84-0.94; p<0.001), respectively.[45] For patients with established ASCVD, both classes reduced MACE by 14% (HR, 0.86, 95% CI, 0.80-0.93; P=0.002). For the individual MACE components, both SGLT-2i and GLP-1RA showed reduced MI by 11% (HR, 0.89; 95% CI, 0.80-0.98; p=0.02) and 9% (HR, 0.91; 05% CI, 0.84-0.98; P=0.01), respectively. In addition, both significantly reduce cardiovascular death by 16% in SGLT-2is (HR, 0.84; 95% CI, 0.75-0.94; p=0.002) and 12% in GLP-1RAs (HR, 0.84; 95% CI 0.75-0.94; P=0.002). However, significant reductions in stroke risk were only found in GLP-1RAs (HR, 0.86; 95% CI, 0.77-0.97; P=0.01) and not in SGLT-2is (HR, 0.97; 95% CI, 0.86-1.10). Additionally, only SGLT-2is significantly reduced hospitalizations for heart failure (HHF) by 31% (HR, 0.69; 95% CI, 0.61-0.79; P<0.001) compared to a non-significant 7% reduction in GLP-1RA (HR, 0.93; 95% CI, 0.83-1.04; P=0.20). However, these results were limited to aggregated study-level data rather than patient-level data. Therefore, differences in patient characteristics could not be ascertained to explain variations in treatment effects.

There have been several retrospective studies that have examined CV outcomes associated with the use of these agents. In CVD-REAL, a large multi-national study that included 309,056 patients across the United States, Norway, Denmark, Sweden, Germany, and the United Kingdom, patients initiating SGLT-2is were compared to a propensity score matched sample of patients initiating other glucose-lowering agents in regards to heart failure hospitalizations and all-cause death.[46] Results were pooled together to provide a weighted summary from all countries. Findings from their results showed a significant reduction in heart failure hospitalizations (HR 0.61, 95% CI: 0.51–0.73), all-cause death (HR 0.49, 95%CI: 0.41–0.57), and a composite of heart failure hospitalization or all-cause death (HR 0.54, 95% CI: 0.48–0.60) compared to other glucose-lowering agents. However, they did not include other relevant CV-related outcomes, such as myocardial infarction, stroke, unstable angina requiring hospitalizations, or coronary revascularizations. In addition, they did not compare SGLT-2is to any specific class. Therefore, conclusions regarding the comparative CV outcomes between SGLT-2is and GLP-1RAs could not be ascertained.

In CVD-REAL 2, a subsequent study of 235,064 patients across 6 countries in the Asia Pacific, the Middle East, and North American regions, initiators of SGLT-2is were compared with a propensity score matched sample of other glucose-lowering agents to also investigate risks for heart failure hospitalization and all-cause death, as well as myocardial infarction and stroke.[47] They found that SGLT-2is were associated with a lower risk of all-cause death (HR 0.51, 95% CI: 0.37 to 0.70), heart failure hospitalizations (HR 0.64, 95% CI: 0.50 to 0.82), a composite of all-cause death and heart failure hospitalizations (HR 0.60, 95% CI: 0.47 to 0.76), myocardial infarction (HR 0.81, 95% CI: 0.74 to 0.88), and stroke (HR 0.68, 95% CI: 0.55 to 0.84) compared to other glucose-lowering agents. While the investigators did improve in their methods by including myocardial infarction and stroke as CV endpoints, they still did not make any specific comparisons between SGLT-2is and specific drug classes. In addition, this study was limited to populations outside of the US.

In a similar study by Paterno et al., using a nationwide sample of commercially insured T2D patients, initiators of canagliflozin were compared to propensity score matched samples of GLP-1RA initiators. Their findings showed that canagliflozin was associated with lower risk of heart failure hospitalizations (HR 0.61, 95% CI: 0.47-0.78), no difference in risk of the composite CV endpoint (myocardial infarction and stroke) (1.03 (0.79-1.35), no difference in the risk of the expanded composite endpoint (primary composite CV endpoint, unstable angina, and coronary hospitalization), and no difference in the individual components of the composite endpoints. While this study did investigate the comparative effects of an SGLT-2i and GLP-1RA, they limited the study to a single agent without inclusion of other agents within the SGLT-2i class.

As current interest has shifted from focusing solely on glycemic endpoints to incorporating CV outcomes of antihyperglycemic treatment to assess their effectiveness, real-world evidence comparing differences in CV outcomes between these two drug classes with demonstrated CV benefit and oADMs as the comparative CV outcomes between each other will be useful for well-informed clinical decision making for patients, payers, and providers.

1.10 STUDY OBJECTIVES AND HYPOTHESIS

The aim of this study is to evaluate and compare patient demographics, clinical characteristics, medication utilization, and CV outcomes among adults with T2D who are newly initiated on SGLT-2is, GLP-1RAs, and oADMs. Specific objectives and null hypotheses of this study include:

1. Describe and determine whether baseline demographics differ between T2D patients newly initiated on SGLT-2is versus oADMs, GLP-1RAs versus oADMs, and SGLT-2is versus GLP-1RAs.

    $H_0$1.1: The difference in age between patients newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$1.2: The difference in age between patients newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$1.3: The difference in age between patients newly initiated on SGLT2is versus GLP-1RAs is not statistically significant.

$H_0$1.4: The difference in gender between patients newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$1.5: The difference in gender between patients newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$1.6: The difference in gender between patients newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$1.7: The difference in the proportion of patients of white race between patients newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$1.8: The difference in the proportion of patients of white race between patients newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$1.9: The difference in the proportion of patients of white race between patients newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$1.10: The difference in the proportion of patients of other race between patients newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$1.11: The difference in the proportion of patients of other race between patients newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$1.12: The difference in the proportion of patients of other race between patients newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$1.13: The difference in the proportion of patients of unknown race between patients newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$1.14: The difference in the proportion of patients of unknown race between patients newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$1.15: The difference in the proportion of patients of unknown race between patients newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

2. Describe and determine whether baseline prevalence of comorbidities differ between T2D patients newly initiated on SGLT-2is versus oADMs, GLP-1RAs versus oADMs, SGLT-2is versus GLP-1RAs.

   $H_0$2.2: The difference in CCI scores between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

   H_o2.3: The difference in CCI scores between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

   $H_0$2.4: The difference in the proportion of patients with a history of CVD between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

   $H_1$2.5: The difference in the proportion of patients with a history of CVD between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

   $H_0$2.6: The difference in the proportion of patients with a history of CVD between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

   $H_0$2.7: The difference in the proportion of patients with a history of MI between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

   $H_1$2.8: The difference in the proportion of patients with a history of MI between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$2.9: The difference in the proportion of patients with a history of MI between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$2.10: The difference in the proportion of patients with a history of stroke between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$2.11: The difference in the proportion of patients with a history of stroke between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$2.12: The difference in the proportion of patients with a history of stroke between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$2.13: The difference in the proportion of patients with a history of TIA between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$2.14: The difference in the proportion of patients with a history of TIA between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$2.15: The difference in the proportion of patients with a history of TIA between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$2.16: The difference in the proportion of patients with unstable angina between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$2.17: The difference in the proportion of patients with unstable angina between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$2.18: The difference in the proportion of patients with unstable angina between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$2.19: The difference in the proportion of patients with angina pectoris between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$2.20: The difference in the proportion of patients with angina pectoris between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$2.21: The difference in the proportion of patients with angina pectoris between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$2.22: The difference in the proportion of patients with heart failure between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$2.23: The difference in the proportion of patients with heart failure between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$2.24: The difference in the proportion of patients with heart failure between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$2.25: The difference in the proportion of patients with PAD between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$2.26: The difference in the proportion of patients with PAD between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$2.27: The difference in the proportion of patients with PAD between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$2.28: The difference in the proportion of patients with atrial fibrillation between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$2.29: The difference in the proportion of patients with atrial fibrillation between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$2.30: The difference in the proportion of patients with atrial fibrillation between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$2.31: The difference in the proportion of patients with hypertension between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$2.32: The difference in the proportion of patients with hypertension between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$2.33: The difference in the proportion of patients with hypertension between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$2.34: The difference in the proportion of patients with CKD between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$2.35: The difference in the proportion of patients with CKD between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$2.36: The difference in the proportion of patients with CKD between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$2.37: The difference in the proportion of patients with microvascular disease between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$2.38: The difference in the proportion of patients with microvascular disease between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$2.39: The difference in the proportion of patients with microvascular disease between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$2.40: The difference in the proportion of patients with dyslipidemia between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$2.41: The difference in the proportion of patients with dyslipidemia between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$2.42: The difference in the proportion of patients with dyslipidemia between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$2.43: The difference in the proportion of patients with obesity between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$2.44: The difference in the proportion of patients with obesity between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$2.45: The difference in the proportion of patients with obesity between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

3. Describe and determine whether baseline medication use differ between T2D patients newly initiated on SGLT-2is versus oADMs, GLP-1RAs versus oADMs, SGLT-2is versus GLP-1RAs.

   $H_0$3.1: The difference in the number of antidiabetic medications used between patients newly initiated on SGLT-2is versus oADMs is not statistically significant.

   $H_0$3.2: The difference in the number of antidiabetic medications used between patients newly initiated on GLP-1RAs versus oADMs is not statistically significant.

   $H_0$3.3: The difference in the number of antidiabetic medications used between patients newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

   $H_0$3.4: The difference in the proportion of patients taking metformin between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

   $H_0$3.5: The difference in the proportion of patients taking metformin between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

   $H_0$3.6: The difference in the proportion of patients taking metformin between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

   $H_0$3.7: The difference in the proportion of patients taking DPP-4is between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

   $H_0$3.8: The difference in the proportion of patients taking DPP-4is between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

   $H_0$3.9: The difference in the proportion of patients taking DPP-4is between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$3.10: The difference in the proportion of patients taking sulfonylureas between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$3.11: The difference in the proportion of patients taking sulfonylureas between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$3.12: The difference in the proportion of patients taking sulfonylureas between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$3.13: The difference in the proportion of patients taking TZDs between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$3.14: The difference in the proportion of patients taking TZDs between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$3.15: The difference in the proportion of patients taking TZDs between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$3.16: The difference in the proportion of patients taking meglinitides between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$3.17: The difference in the proportion of patients taking meglinitides between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$3.18: The difference in the proportion of patients taking meglinitides between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$3.19: The difference in the proportion of patients taking insulin between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$3.20: The difference in the proportion of patients taking insulin between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

H_o3.21: The difference in the proportion of patients taking insulin between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

H_o3.22: The difference in the proportion of patients taking ACEis, between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$3.23: The difference in the proportion of patients taking ACEis, between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$3.24: The difference in the proportion of patients taking ACEis, between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$3.25: The difference in the proportion of patients taking ARBs between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$3.26: The difference in the proportion of patients taking ARBs between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$3.27: The difference in the proportion of patients taking ARBs between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$3.28: The difference in the proportion of patients taking beta blockers between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$3.29: The difference in the proportion of patients taking beta blockers between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$3.30: The difference in the proportion of patients taking beta blockers between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$3.31: The difference in the proportion of patients taking calcium channel blockers (CCBs) between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$3.32: The difference in the proportion of patients taking CCBs between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$3.33: The difference in the proportion of patients taking CCBs between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$3.34: The difference in the proportion of patients taking thiazides between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$3.35: The difference in the proportion of patients taking thiazides between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$3.36: The difference in the proportion of patients taking thiazides between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$3.37: The difference in the proportion of patients taking loop diuretics between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$3.38: The difference in the proportion of patients taking loop diuretics between

those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$3.39: The difference in the proportion of patients taking loop diuretics between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$3.40: The difference in the proportion of patients taking nitrates between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$3.41: The difference in the proportion of patients taking nitrates between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$3.42: The difference in the proportion of patients taking nitrates between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$3.43: The difference in the proportion of patients taking anticoagulants between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$3.44: The difference in the proportion of patients taking anticoagulants between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$3.45: The difference in the proportion of patients taking anticoagulants between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$3.46: The difference in the proportion of patients taking antiplatelets between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$3.47: The difference in the proportion of patients taking antiplatelets between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$3.48: The difference in the proportion of patients taking antiplatelets between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$3.49: The difference in the proportion of patients taking statins between those who are newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$3.50: The difference in the proportion of patients taking statins between those who are newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$3.51: The difference in the proportion of patients taking statins between those who are newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

4. Describe and determine whether HbA1c prior to initiation of study medications differs between T2D patients newly initiated on SGLT-2is versus oADMs, GLP-1RAs versus oADMs, SGLT-2is versus GLP-1RAs.

    $H_0$4.1: The difference in proportion of patients missing HbA0c values newly initiated on SGLT-2is versus oADMs is not statistically significant.

    $H_0$4.2: The difference in proportion of patients missing HbA1c values newly initiated on GLP-1RAs versus oADMs is not statistically significant.

    $H_0$4.3: The difference in proportion of patients missing HbA1c values newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.

    $H_0$4.4: The difference in HbA1c between patients newly initiated on SGLT-2is versus oADMs is not statistically significant.

    $H_0$4.5: The difference in HbA1c between patients newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$4.6: The difference in HbA1c between patients newly initiated SGLT-2is versus GLP-1RAs is not statistically significant.

5. Determine whether the cumulative incidence or hazard of CV outcomes differ between T2D patients newly initiated on SGLT-2is versus oADMs, GLP-1RAs versus oADMs, SGLT-2is versus GLP-1RAs.

   $H_0$5.1: The difference in the cumulative incidence or hazard of the composite CV endpoint between patients newly initiated on SGLT-2is versus oADMs is not statistically significant.

   $H_0$5.2: The difference in the cumulative incidence or hazard of the composite CV endpoint between patients newly initiated on GLP-1RAs versus oADMs is not statistically significant.

   $H_0$5.3: The difference in the cumulative incidence or hazard of the composite CV endpoint between patients newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

   $H_0$5.4 The difference in the cumulative incidence or hazard of hospitalizations for heart failure between patients newly initiated on SGLT-2is versus oADMs is not statistically significant.

   $H_0$5.5: The difference in the cumulative incidence or hazard of hospitalizations for heart failure between patients newly initiated on GLP-1RAs versus oADMs is not statistically significant.

   $H_0$5.6: The difference in the cumulative incidence or hazard of hospitalizations for heart failure between patients newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

   $H_0$5.7: The difference in the cumulative incidence or hazard of MI between patients newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$5.8: The difference in the cumulative incidence or hazard of MI between patients newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$5.9: The difference in the cumulative incidence or hazard of MI between patients newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

$H_0$5.10: The difference in the cumulative incidence or hazard of unstable angina requiring hospitalization between patients newly initiated on SGLT-2is versus oADMs is not statistically significant.

$H_0$5.11: The difference in the cumulative incidence or hazard of unstable angina requiring hospitalization between patients newly initiated on GLP-1RAs versus oADMs is not statistically significant.

$H_0$5.12: The difference in the cumulative incidence or hazard of unstable angina requiring hospitalization between patients newly initiated on SGLT-2is versus GLP-1RAs is not statistically significant.

Chapter 2: Methodology

2.1 Study Design

This population-based study used a retrospective observational new user cohort study design to assess the effects of initiating SGLT-2is versus oADMs, GLP-1RAs versus oADMs, SGLT-2is versus GLP-1RAs on CV outcomes in patients with T2D. An active comparator, new user or incident user study design was selected over a prevalent user study design to eliminate the need to adjust for confounding due to pretreatment effects and overestimating medication benefits and/or safety.[48] In addition, focusing on new users provided the ability to capture all outcome-related events occurring after the initial start of therapy as well as reduced the potential for confounding bias by varying disease severity.

2.2 Data Source

This study utilized administrative claims and electronic health record (EHR) data from April 1, 2012 through December 31, 2018. Patient-level data were extracted from the Virtual Data Warehouse (VDW), which houses pharmacy and medical claims for the Scott and White Health Plan (SWHP), and EHR data from the Baylor Scott and White Health (BSWH) System. SWHP has approximately 415,000 covered lives, geographically located within the central and northern Texas regions and includes a payer mix of commercial, Medicare and Medicaid populations. BSWH is a non-profit, integrated delivery network, which includes a network of 48 acute care hospitals and more than 900 patient care sites with approximately 6,000 physicians and other healthcare providers. Unique member identification numbers were used to longitudinally link pharmacy and medical claims to patient enrollment and medical care data containing demographic information. Pharmacy claims provided details from all dispensed prescriptions, including drug name, National Drug Code (NDC), prescription filled date, quantity dispensed, days supplied, and prescriber information. Medical claims provided detailed information on inpatient and outpatient services, including encounter dates, place of service, procedure codes, and up to 5 International

Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Edition, Clinical Modification (ICD-10-CM) diagnosis codes per episode of care. This study was approved by the Baylor Scott & White Health and the University of Texas institutional review board following expedited review.

2.3 SAMPLE SELECTION

Patients were included if they were aged 18 years or older at the time of cohort entry, a diagnosis of T2D, at least 12 months of continuous health plan enrollment in the pre-index (baseline) period, and at least one prescription claim for either a SGLT-2i, GLP-1RA, or oADM (metformin, DPP-4is, sulfonylureas, TZDs, meglinitides, and insulin) filled between April 1, 2013 through December 31, 2018 (index period). The first prescription date for either a SGLT-2i, GLP-1RA, or oADM during the index period was referred to as the index date. A diagnosis of T2D was defined as having at least one inpatient or outpatient medical claim with an ICD-9-CM of 250.x0, 250.x2, or ICD-10-CM of E11.

Only new users, defined as having a prescription claim for either a SGLT-2i, GLP-1RA, or oADM with a wash-out period with no prescription claim within the same drug class during the 12-month baseline period, were included in the study. Patients were divided into three groups using a hierarchical approach according to the index medication identified: SGLT-2i, GLP-1RA, and oADM. Patients were first assessed for inclusion for either the SGLT-2i or GLP-1RA group. The remaining patients were then considered for the oADM group. In cases where patients initiated more than one oADM on the day of cohort entry, index medication was selected at random.

Patients were excluded in the SGLT-2i group if a prescription claim for a GLP-1RA was identified in the 12-month baseline period to eliminate probable carryover effects of prior competitor use. Consideration of excluding GLP-1RA patients with a prior history of SGLT-2i use was not necessary, since the FDA-approval date of the first SGLT-2i marketed in the US, canagliflozin, was March 29, 2013. Other exclusion criteria included a diagnosis of T1D.

2.4 BASELINE VARIABLES

Demographic and clinical characteristics were assessed using medical and pharmacy claims and EHR data during the 12-month baseline period. Demographic variables include age, gender, and race. Age was calculated at the time of index date. Clinical characteristics include HbA1c, comorbidities, and glucose-lowering and CV-related medication utilization. Comorbidities were identified within medical claims by ICD-9-CM, ICD-10-CM, and Current Procedural Terminology (CPT) codes. Relevant comorbidities included history of CVD, MI, stroke, TIA, unstable angina, angina pectoris, heart failure, PAD, atrial fibrillation, hypertension, CKD, microvascular disease, history of coronary revascularization procedures, dyslipidemia, obesity, and conditions found in the in the CCI. CCI was calculated using ICD-9-CM/ICD-10-CM diagnosis codes using the University of Manitoba definitions of disorders.[49] Medications were identified within pharmacy claims using NDC numbers and a string-search of generic and brand medication names (Appendix A). A summary of study variables is provided in Table 2.4.1.

Table 2.4.1 Baseline Variables

Objective 1: Describe and compare baseline demographic and clinical characteristics between patients who are newly initiated on SGLT-2is versus oADMs, GLP-1RAs versus oADMs, and SGLT-2is versus GLP-1RAs.	**Demographics**			
	Category	**Variable**	**Measurement Level**	**Data Source**
	Independent	Age at index • Mean (SD) or median (IQR)	Continuous	Demographics
	Independent	Gender • Count (%) Female	Categorical	Demographics
	Independent	Race • Count (%) White • Count (%) Other • Count (%) Unknown	Categorical	Demographics
Objective 2: Describe and determine whether baseline prevalence of comorbidities differ between T2D patients who are newly initiated on SGLT-2is versus oADMs, GLP-1RAs versus oADMs, SGLT-2is versus GLP-1RAs.	**Comorbidities**			
	Category	**Variable**	**Measurement Level**	**Data Source**
	Independent	CCI score at baseline • Mean (SD) or median (IQR)	Continuous	Medical Claims
	Independent	History of CVD at baseline • Count (%) Yes	Categorical	Medical Claims
	Independent	History of MI at baseline • Count (%) Yes	Categorical	Medical Claims
	Independent	History of stroke at baseline • Count (%) Yes	Categorical	Medical Claims
	Independent	History of TIA at baseline • Count (%) Yes	Categorical	Medical Claims
	Independent	Unstable angina at baseline • Count (%) Yes	Categorical	Medical Claims
	Independent	Angina pectoris at baseline • Count (%) Yes	Categorical	Medical Claims
	Independent	Heart failure at baseline • Count (%) Yes	Categorical	Medical Claims
	Independent	PAD at baseline • Count (%) Yes	Categorical	Medical Claims
	Independent	Atrial fibrillation at baseline • Count (%) Yes	Categorical	Medical Claims
	Independent	Hypertension at baseline • Count (%) Yes	Categorical	Medical Claims
	Independent	CKD at baseline • Count (%) Yes	Categorical	Medical Claims
	Independent	Microvascular comorbidities at baseline • Count (%) Yes	Categorical	Medical Claims
	Independent	History of coronary revascularization at baseline • Count (%) Yes	Categorical	Medical Claims
	Independent	Dyslipidemia at baseline • Count (%) Yes	Categorical	Medical Claims
	Independent	Obesity at baseline • Count (%) Yes	Categorical	Medical Claims

Objective 3: Describe and determine whether baseline medication use differ between T2D patients who are newly initiated on SGLT-2is versus oADMs, GLP-1RAs versus oADMs, SGLT-2is versus GLP-1RAs.	**Medication Utilization**			
	Category	**Variable**	**Measurement Level**	**Data Source**
	Independent	Number of antidiabetic agents at baseline • Mean (SD)	Continuous	Prescription Claims
	Independent	Metformin use at baseline • Count (%) Yes	Categorical	Prescription Claims
	Independent	DPP-4i use at baseline • Count (%) Yes	Categorical	Prescription Claims
	Independent	SU use at baseline • Count (%) Yes	Categorical	Prescription Claims
	Independent	TZD use at baseline • Count (%) Yes	Categorical	Prescription Claims
	Independent	Meglinitide use at baseline • Count (%) Yes	Categorical	Prescription Claims
	Independent	Proportion of patients taking insulin at baseline • Count (%) Yes	Categorical	Prescription Claims
	Independent	ACEi use at baseline • Count (%) Yes	Categorical	Prescription Claims
	Independent	ARB use at baseline • Count (%) Yes	Categorical	Prescription Claims
	Independent	Beta blocker use at baseline • Count (%) Yes	Categorical	Prescription Claims
	Independent	CCB at baseline • Count (%) Yes	Categorical	Prescription Claims
	Independent	Thiazide use at baseline • Count (%) Yes	Categorical	Prescription Claims
	Independent	Loop diuretic use at baseline • Count (%) Yes	Categorical	Prescription Claims
	Independent	Nitrate use at baseline • Count (%) Yes	Categorical	Prescription Claims
	Independent	Anticoagulant use at baseline • Count (%) Yes	Categorical	Prescription Claims
	Independent	Antiplatelet use at baseline • Count (%) Yes	Categorical	Prescription Claims
	Independent	Statin use at baseline • Count (%) Yes	Categorical	Prescription Claims
Objective 4: Describe and determine whether HbA1c prior to initiation of study medications differs between T2D patients newly initiated on SGLT-2is versus oADMs, GLP-1RAs versus oADMs, SGLT-2is versus GLP-1RAs.	**Medication Utilization**			
	Category	**Variable**	**Measurement level**	**Data Source**
	Independent	HbA1c at baseline • Mean (SD) or median (IQR)	Continuous	Electronic health record

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium-channel blocker; CCI = Charlson Comorbidity Index; CKD = chronic kidney disease; CV = cardiovascular; DPP-4i = dipeptidyl peptidase-4 inhibitor; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = hemoglobin A1c; HF = heart failure; oADM = antidiabetic medications; MI = myocardial infarction; PAD = peripheral artery disease; SGLT-2i = sodium-glucose cotransporter-2 inhibitor; SU = sulfonylurea; TIA = transient ischemic attack; TZD = thiazolidinediones

2.5 OBSERVATION PERIOD

Follow-up began on the day after index date for all three cohorts. Patients were followed using an on-treatment approach until occurrence of a study outcome event, treatment discontinuation, switch to a comparator, end of continuous health plan enrollment, or end of the study period (December 31, 2018), whichever came first. Treatment discontinuation was defined as >60-day persistence gap. Persistence was calculated as the days from the day of first prescription claim to the day of first occurrence of prescription fill gap. End of continuous health plan enrollment was defined as a gap in continuous health plan enrollment of >45 days.

2.6 STATISTICAL ANALYSIS

2.6.1 Baseline Demographic and Clinical Characteristics

Descriptive statistics were performed on all variables. Continuous variables were described in means with standard deviation (SD) or medians with interquartile range (IQR), and categorical variables were described in frequency with percentages. Student t-test or Mann-Whitney U test were used for continuous measures and chi-square analysis for categorical measures to detect differences between groups. Three separate multivariable logistic regression models were used to estimate propensity scores and predict the probability of being initiated on a SGLT-2i versus oADM, GLP-1RA versus oADM, and SGLT-2i versus GLP-1RA, controlling for all of the listed covariates listed in Table 2.1, which were assumed to have an effect on treatment assignment or study outcomes. The propensity scores, using a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score, were used to 1:1 match patients using a pairwise approach and

nearest neighbor greedy algorithm to adjust for confounders and balance baseline patient characteristics between treatment groups. Pairwise comparisons of patient demographics and clinical characteristics between SGLT-2is versus oADMs, GLP-1RAs versus oADMs and SGLT-2is versus GLP-1RAs were compared before and after matching. A standardized difference of greater than 10% was considered a significant imbalance between groups.

2.6.2 Cardiovascular Outcomes

Primary end points were a composite CV outcome comprised of hospitalizations for acute MI, stroke, unstable angina, and coronary revascularization, as well as hospitalization for heart failure. A composite end point was selected for the primary outcome in order to accumulate more events to increase reliable statistical power. The use of singular event end points would require a substantially larger sample population than we anticipate from a regional health plan population such as SWHP. Secondary end points were the individual components of the CV composite.

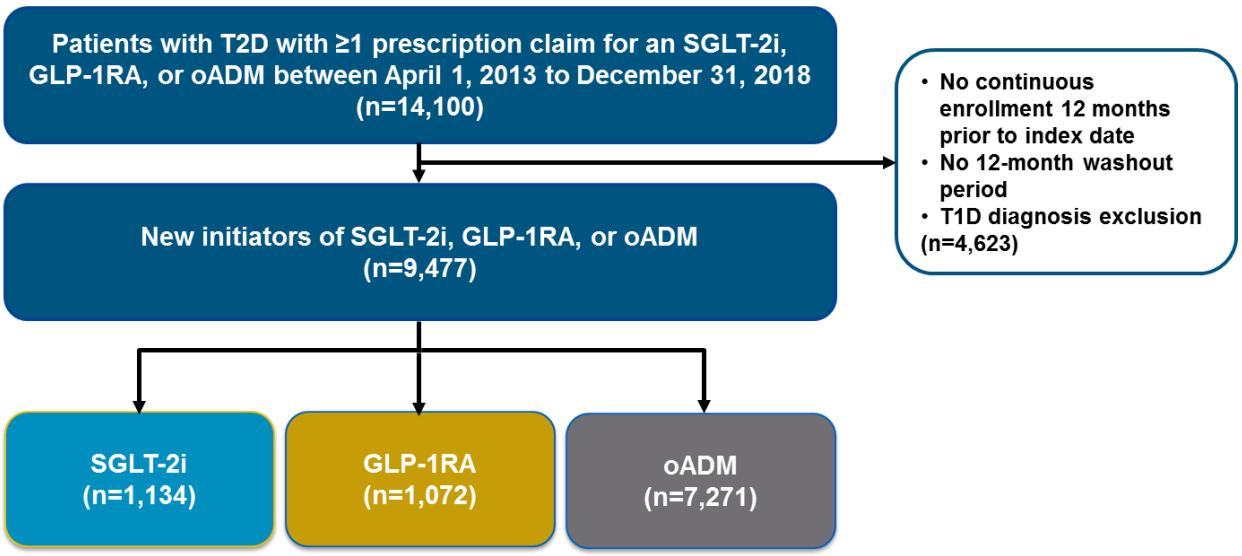
Cumulative incidence of all CV outcome variables were described using Kaplan-Meier failure plots and compared using log-rank tests and cox proportional hazards regression models. Incident event rates for all outcomes were described for each cohort as the number of first occurrence of the outcome events divided by the total number of person-years at risk. Hazard Ratios (HR) with 95% confidence intervals (CI) were reported for each outcome for all pairwise comparisons. All data manipulation and analyses were performed using SAS version 9.4 software (SAS institute, Cary, North Carolina) using an alpha < 0.05 as the criterion for statistical significance.

Chapter 3: Results

3.1 Study Sample

From April 1, 2013 through December 31, 2018, a total of 14,100 patients with T2D who were new initiators of either an SGLT-2i, GLP-1RA, or oADM were identified. After applying study exclusions, 9,477 patients remained: 1,134 SGL-2is initiators, 1,072 GLP-1RA initiators, and 7,271 oADM initiators. Figure 3.1 provides the flow chart for patient selection.

Figure 3.1.1: Patient selection flow chart



GLP-1RA = glucagon-like peptide-1 receptor agonist; oADM = other antidiabetic medication; T1D = type 1 diabetes; T2D = type 2 diabetes; SGLT-2i = sodium-glucose cotransporter-2 inhibitor

3.2 Baseline Demographics and Clinical Characteristics

Table 3.2.1 describes and compares the pre-match baseline patient characteristics within each cohort.

Table 3.2.1 Baseline Patient Characteristics Pre-Match

Variables n=patients	Cohort 1			Cohort 2			Cohort 3		
	SGLT-2i (n=1134)	oADM (n=7271)	p-value	GLP-1RA (n=1072)	oADM (n=7271)	p-value	SGLT-2i (n=1134)	GLP-1RA (n=1072)	p-value
Demographics									
Age, years, median (IQR)	55.0 (14.0)	60.0 (20.0)	**<0.001**	55.0 (15.0)	60.0 (20.0)	**<0.001**	55.0 (14.0)	55.0 (15.0)	0.27
Gender									
Female	554 (48.9)	3501 (48.2)	0.66	640 (57.9)	3501 (48.2)	**<0.001**	554 (48.9)	640 (59.7)	**<0.001**
Race									
White	442 (39.0)	3863 (53.1)	**<0.001**	433 (40.4)	3863 (53.1)	**<0.001**	442 (39.0)	433 (40.4)	0.50
Other	106 (9.4)	891 (12.3)	**0.005**	106 (9.9)	891 (12.3)	**0.03**	106 (9.4)	106 (9.9)	0.67
Unknown	586 (51.7)	2517 (34.6)	**<0.001**	533 (49.7)	2517 (34.6)	**<0.001**	586 (51.7)	533 (49.7)	0.36
Comorbidities									
CCI, median (IQR)	2.0 (2.0)	1.0 (2.0)	0.7706	2.0 (2.0)	1.0 (2.0)	**0.002**	2.0 (2.0)	2.0 (2.0)	**0.01**
CVD History	148 (13.1)	1682 (23.1)	**<0.001**	154.0 (14.4)	1682 (23.1)	**<0.001**	148 (13.1)	154.0 (14.4)	0.37
MI	10 (0.9)	145 (2.0)	**<0.001**	12.0 (1.1)	145 (2.0)	**0.049**	10 (0.9)	12.0 (1.1)	0.57
Stroke	18 (1.6)	252 (3.5)	**<0.001**	16.0 (1.5)	252 (3.5)	**0.001**	18 (1.6)	16.0 (1.5)	0.86
TIA	17 (1.5)	136 (1.9)	0.38	15.0 (1.4)	136 (1.9)	0.28	17 (1.5)	15.0 (1.4)	0.84
Unstable angina	82 (7.2)	987 (13.6)	**<0.001**	73.0 (6.8)	987 (13.6)	**<0.001**	82 (7.2)	73.0 (6.8)	0.70
Angina pectoris	11 (1.0)	140 (1.9)	**0.02**	9.0 (0.8)	140 (1.9)	**0.01**	11 (1.0)	9.0 (0.8)	0.75
Heart failure	47 (4.1)	702 (9.7)	**<0.001**	62.0 (5.8)	702 (9.7)	**<0.001**	47 (4.1)	62.0 (5.8)	0.08
PAD	13 (1.2)	179 (2.5)	**0.006**	18.0 (1.7)	179 (2.5)	0.12	13 (1.2)	18.0 (1.7)	0.29
Atrial fibrillation	12 (1.1)	332 (4.6)	**<0.001**	12.0 (1.1)	332 (4.6)	**<0.001**	12 (1.1)	12.0 (1.1)	0.89
Hypertension	898 (79.2)	5690 (78.3)	0.48	875.0 (81.6)	5690 (78.3)	**0.01**	898 (79.2)	875.0 (81.6)	0.15
CKD	48 (4.2)	609 (8.4)	**<0.001**	99.0 (9.2)	609 (8.4)	0.35	48 (4.2)	99.0 (9.2)	**<0.001**
Microvascular disease	649 (57.2)	2813 (38.7)	**<0.001**	648.0 (60.5)	2813 (38.7)	**<0.001**	649 (57.2)	648.0 (60.5)	**0.13**
Dyslipidemia	934 (82.4)	5041 (69.3)	**<0.001**	838.0 (78.2)	5041 (69.3)	**<0.001**	934 (82.4)	838.0 (78.2)	**0.01**
Obesity	508 (44.8)	2746 (37.8)	**<0.001**	616.0 (57.5)	2746 (37.8)	**<0.001**	508 (44.8)	616.0 (57.5)	**<0.001**

Antidiabetic medications									
Number of antidiabetic medications, median (IQR)	2.0 (2.0)	0.0 (1.0)	**<0.001**	2.0 (2.0)	0.0 (1.0)	**<0.001**	2.0 (2.0)	2.0 (2.0)	**<0.001**
Metformin	908 (80.1)	1450 (19.9)	**<0.001**	787.0 (73.4)	1450 (19.9)	**<0.001**	908 (80.1)	787.0 (73.4)	**<0.001**
DPP-4i	358 (31.6)	240 (3.3)	**<0.001**	252.0 (23.5)	240 (3.3)	**<0.001**	358 (31.6)	252.0 (23.5)	**<0.001**
SU	581 (51.2)	992 (13.6)	**<0.001**	477.0 (44.5)	992 (13.6)	**<0.001**	581 (51.2)	477.0 (44.5)	**0.002**
TZD	104 (9.2)	76 (1.1)	**<0.001**	69.0 (6.4)	76 (1.1)	**<0.001**	104 (9.2)	69.0 (6.4)	**0.02**
Meglinitides	11 (1.0)	5 (0.1)	**<0.001**	8.0 (0.8)	5 (0.1)	**<0.001**	11 (1.0)	8.0 (0.8)	0.57
Insulin	370 (32.6)	484 (6.7)	**<0.001**	442.0 (41.2)	484 (6.7)	**<0.001**	370 (32.6)	442.0 (41.2)	**<0.001**
CV-related medications									
ACEi	561 (49.5)	2706 (37.2)	**<0.001**	511.0 (47.7)	2706 (37.2)	**<0.001**	561 (49.5)	511.0 (47.7)	0.40
ARB	294 (25.9)	1297 (17.8)	**<0.001**	316.0 (29.5)	1297 (17.8)	**<0.001**	294 (25.9)	316.0 (29.5)	0.06
Beta Blocker	305 (26.9)	2267 (31.2)	**0.004**	324.0 (30.2)	2267 (31.2)	0.53	305 (26.9)	324.0 (30.2)	0.08
CCB	230 (20.3)	1509 (20.8)	0.72	248.0 (23.1)	1509 (20.8)	0.07	230 (20.3)	248.0 (23.1)	0.10
Thiazides	361 (31.8)	2002 (27.5)	**0.003**	396.0 (36.9)	2002 (27.5)	**<0.001**	361 (31.8)	396.0 (36.9)	**0.01**
Loop Diuretic	85 (7.5)	812 (11.2)	**0.002**	110.0 (10.3)	812 (11.2)	0.38	85 (7.5)	110.0 (10.3)	**0.02**
Nitrate	45 (4.0)	347 (4.8)	0.23	52.0 (4.9)	347 (4.8)	0.91	45 (4.0)	52.0 (4.9)	0.31
Anticoagulant	29 (2.6)	333 (4.6)	**0.002**	24.0 (2.2)	333 (4.6)	**<0.001**	29 (2.6)	24.0 (2.2)	0.63
Antiplatelet	82 (7.2)	453 (6.2)	0.20	85.0 (7.9)	453 (6.2)	**0.04**	82 (7.2)	85.0 (7.9)	0.54
Statin	786 (69.3)	3447 (47.4)	**<0.001**	708.0 (66.0)	3447 (47.4)	**<0.001**	786 (69.3)	708.0 (66.0)	0.10
Hemoglobin A1C									
Patients with HbA1c Available	334 (29.5)	2564 (36.3)	**<0.001**	304.0 (28.4)	2564 (35.3)	**<0.001**	334 (29.5)	304.0 (28.4)	0.57
HbA1c, median (IQR)	8.8 (1.9)	7.6 (2.1)	**<0.001**	8.4 (1.9)	7.6 (2.1)	**<0.001**	8.8 (1.9)	8.4 (1.9)	**0.02**

Data are n (%) unless otherwise stated.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCB = Calcium channel blocker; CCBs = calcium-channel blocker; CCI = Charlson Comorbidity Index; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DPP-4i = dipeptidyl peptidase-4 inhibitor; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = hemoglobin A1c; IQR = interquartile range; oADM = other antidiabetic medication; MI = myocardial infarction; PAD = peripheral artery disease; SGLT-2i = sodium-glucose cotransporter-2 inhibitor; SU = sulfonylurea; TIA = transient ischemic attack; TZD = thiazolidinediones

3.2.1 Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Antidiabetic Medication Classes

Prior to propensity score matching, patients initiating SGLT-2is were younger (median [IQR]: 55.0 [14.0] versus 60.0 [20.0] years; p<0.001), had lower prevalence of CVD (13.1% versus 23.1%; p<0.001) and CKD (4.2% versus 8.4%; p<0.001), lower baseline utilization of beta-blockers (26.9% versus 31.2%; p=0.004), loop diuretics (7.5% versus 11.2%; p<0.001), and anticoagulants (2.6% versus 4.6%; p=0.002) compared to patients initiating oADMs. However, they were more likely to have microvascular disease (57.2% versus 38.7%; p<0.001), dyslipidemia (82.4% versus 69.3%; p<0.001), obesity (50.4% versus 42.7%; p<0.001), had higher baseline utilization of antihyperglycemic agents (median [IQR]: 2.0 [2.0] versus 0.0 [1.0]; p<0.001), ACEis (49.5% versus 37.2%; p<0.001), ARBs (25.9% versus 17.8%; p<0.001), statins (69.3% versus 47.4%; p<0.001), and had higher HbA1c (median [IQR]: 8.8 [1.9] versus 7.6 [2.1] mg/dL; p<0.001).

3.2.2 Glucagon-like Peptide-1 Receptor Agonists Versus Other Antidiabetic Medication Classes

Prior to propensity score matching, patients initiating GLP-1RAs were younger (median [IQR]: 55.0 [15.0] versus 60.0 [20.0] years; p<0.001), more female (59.7% versus 48.2%; p<0.001), had lower prevalence of CVD (14.4% versus 23.1%; p<0.001), and lower baseline utilization of anticoagulants (2.2% versus 4.6%; p=0.002) and antiarrhythmics (2.5% versus 3.7%; p=0.048) compared to patients initiating oADMs. However, they were more likely to have higher CCI scores (median [IQR]: 2.0 [2.0] versus 1.0 [2.0]; p<0.002), higher prevalence of hypertension (81.6% versus 78.3%; p=0.01), microvascular disease (57.2% versus 38.7%; p<0.001), dyslipidemia (78.2% versus 69.3%; p<0.001), obesity (57.5% versus 42.7%; p<0.001), had higher baseline utilization of antihyperglycemic agents (median [IQR]: 2.0 [2.0] versus 0.0 [1.0]; p<0.001), ACEis (47.7% versus 37.2%; p<0.001), ARBs (29.5% versus 17.8%; p<0.001), thiazide

diuretics (36.9% versus 27.5%; p<0.001), statins (66.0% versus 47.4%; p<0.001), and had higher HbA1c (median [IQR]: 8.4 [1.9] versus 7.6 [2.1] mg/dL; p<0.001).

3.2.3 Sodium-Glucose Cotransporter-2 Inhibitors Versus Glucagon-like Peptide-1 Receptor Agonists

Prior to propensity score matching, patients initiating SGLT-2is were more female (48.9% versus 59.7%; p<0.001), had lower prevalence of CKD (4.2% versus 9.2%; p<0.001), nephropathy (41.5% versus 46.6%; p=0.02), and lower baseline utilization of sulfonylureas (51.2% versus 44.5%; p0.002), insulin (32.6% versus 41.2%; p<0.001), thiazide diuretics (31.8% versus 36.9%; p=0.02), and loop diuretics (7.5% versus 10.3%; p=0.02), compared to patients initiating GLP-1RAs. However, they were more likely to had higher prevalence of dyslipidemia (82.4% versus 78.2%; p=0.01), had higher baseline utilization of metformin (80.1%% versus 73.4%; p<0.001), DPP-4is (31.6% versus 23.5%; p<0.001), and TZD (9.2% versus 6.4%; p=0.02), and had higher HbA1c (median [IQR]: 8.8 [1.9] versus 8.4 [1.9] mg/dL; p=0.02).

3.3 CARDIOVASCULAR OUTCOMES

Table 3.3.1 shows post-match comparisons of baseline characteristics within each cohort.

Table 3.3.1 Baseline Patient Characteristics Post-Match

Variables n=patients	Cohort 1			Cohort 2			Cohort 3		
	SGLT-2i (n=815)	oADM (n=815)	STD Difference	GLP-1RA (n=817)	oADM (n=817)	STD Difference	SGLT-2i (n=947)	GLP-1RA (n=947)	STD Difference
Demographics									
Age, years, median (IQR)	56.0 (14.0)	58.0 (18.0)	-0.1	55.0 (14.0)	56.0 (16.0)	0.1	55.0 (14.0)	55.0 (15.0)	0.1
Gender									
Female	48.8	48.8	0.0	58.0	58.0	0.0	57.7	57.7	0.0
Comorbidities									
CCI, median (IQR)	2.0 (2.0)	2.0 (2.0)	-0.1	2.0 (2.0)	2.0 (2.0)	0.0	2.0 (2.0)	2.0 (15.0)	0.0
History of CVD	14.8	17.9	0.0	15.3	16.3	0.0	12.0	12.8	0.0
MI	0.9	0.9	0.1	1.4	1.0	0.0	0.8	1.2	0.0
Stroke	2.0	2.1	0.0	1.2	1.4	0.0	1.4	1.5	0.0
Unstable angina	8.5	10.4	0.1	8.1	9.0	0.0	6.3	7.0	0.0
Heart failure	4.5	5.8	0.1	6.0	6.8	0.0	4.4	4.1	0.0
PAD	1.4	1.7	0.0	1.8	1.7	0.0	1.2	1.3	0.0
Atrial fibrillation	1.4	1.2	0.0	1.5	1.6	0.01	1.0	1.1	0.0
Hypertension	79.8	80.9	0.0	81.0	80.3	0.0	79.0	80.3	0.0
CKD	4.8	6.5	0.1	9.1	9.5	0.0	4.5	4.9	0.0
Microvascular Disease	51.7	49.7	0.0	55.0	50.0	0.1	58.4	58.3	0.0
Dyslipidemia	81.2	82.2	0.1	76.6	76.9	0.0	80.6	79.0	0.0
Obesity	48.6	46.9	0.0	58.2	58.7	0.0	54.6	59.1	0.1
Antidiabetic medications									
Number of antidiabetic medications, median (IQR)	2.0 (1.0)	2.0 (1.0)	0.0	2.0 (1.0)	2.0 (1.0)	0.0	2.0 (2.0)	2.0 (2.0)	0.1
Metformin	73.0	74.4	0.0	66.8	70.4	0.1	78.8	77.5	0.0
DPP-4i	22.2	18.6	-0.1	18.4	16.3	0.1	29.7	25.5	0.1
SU	44.2	44.9	0.0	38.8	38.3	0.0	49.7	47.4	0.1
TZD	5.0	4.8	0.0	5.0	4.1	0.1	9.1	7.2	0.1
Insulin	24.4	24.7	0.0	31.2	27.7	0.1	34.2	37.4	0.1
CV-related medications									
ACEi	49.2	50.4	0.0	47.0	47.5	0.0	48.8	47.3	0.0

ARB	25.3	25.0	0.0	27.4	27.4	0.0	26.4	27.8	0.0
Beta Blocker	20.9	22.4	0.1	31.3	31.2	0.0	26.6	28.1	0.0
CCB	20.9	22.4	0.0	22.5	23.1	0.0	20.4	22.0	0.1
Thiazide Diuretic	32.9	32.3	0.0	36.3	34.2	0.0	33.2	34.6	0.0
Loop Diuretic	2.8	2.7	0.1	11.7	12.4	0.0	7.9	8.2	0.0
Anticoagulant	2.8	2.7	0.0	2.7	2.3	0.0	2.2	2.0	0.0
Statin	68.2	70.3	0.0	62.5	63.6	0.0	68.3	66.1	0.1

Data are n (%) unless otherwise stated.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCB = Calcium channel blocker; CCBs = calcium-channel blocker; CCI = Charlson Comorbidity Index; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DPP-4i = dipeptidyl peptidase-4 inhibitor; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = hemoglobin A1c; IQR = interquartile range; oADM = other antidiabetic medication; MI = myocardial infarction; PAD = peripheral artery disease; SGLT-2i = sodium-glucose cotransporter-2 inhibitor; SU = sulfonylurea; TIA = transient ischemic attack; TZD = thiazolidinediones

After propensity score matching, relevant patient characteristics included in all three propensity score models were well balanced with standardized differences ≤10%. There were 815 matched pairs in Cohort 1 (SGLT-2i versus oADM), 817 matched pairs in Cohort 2 (GLP-RA versus oADM), and 947 matched pairs in Cohort 3 (SGLT-2i versus GLP-1RA).

3.3.1 Primary Cardiovascular Outcomes

Table 3.3.1.1 shows the associated risks for the composite CV outcome and hospitalization for heart failure for patients in each pairwise propensity score matched cohort.

Table 3.3.1.1 Risk of composite cardiovascular outcome and hospitalization for heart failure for patients within each pairwise propensity score matched cohort

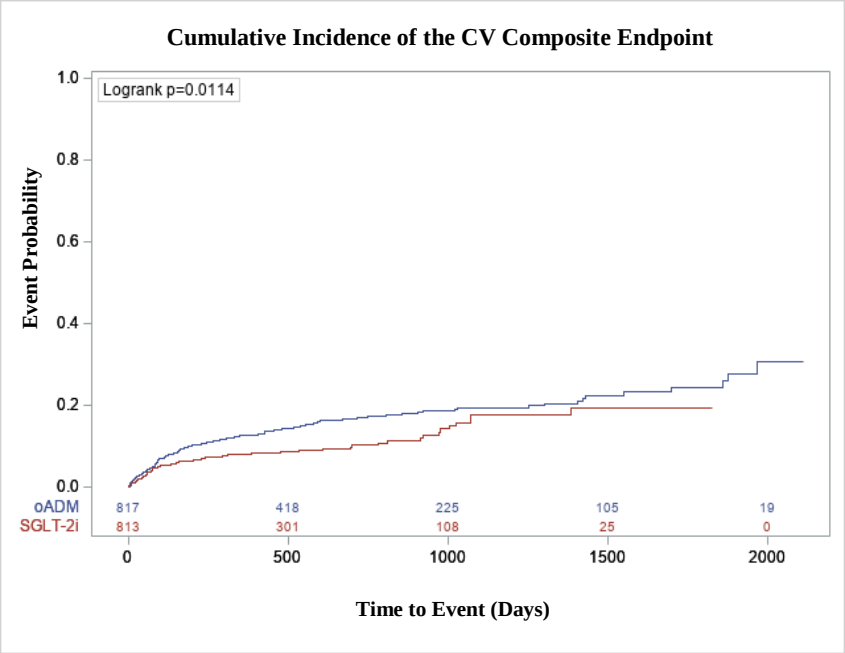
	Cohort 1 (n=818 pairs)			**Cohort 2 (n=815 pairs)**			**Cohort 3 (n=947 pairs)**		
CV Outcomes	**SGLT-2i**	**oADM**	p-value	**GLP-1RA**	**oADM**	p-value	**SGLT-2i**	**GLP-1RA**	p-value
CV Composite Endpoint									
Follow-up, years	1058	1530		921	1521		1249	1090	
Incidence rate*	7.0	8.5		7.6	8.2		6.2	6.2	
Hazard Ratio (95% CI)	0.69 (0.52-0.92)		0.01	0.70 (0.52-0.94)		0.02	1.03 (0.72-1.43)		0.86
Heart failure hospitalization									
Follow-up, years	1096	1679		956	1629		1289	1124	
Incidence rate*	4.7	6.3		6.4	6.9		4.1	4.9	
Hazard Ratio (95% CI)	0.66 (0.47-0.93)		0.02	0.79 (0.57-1.08)		0.14	0.88 (0.60-1.29)		0.51

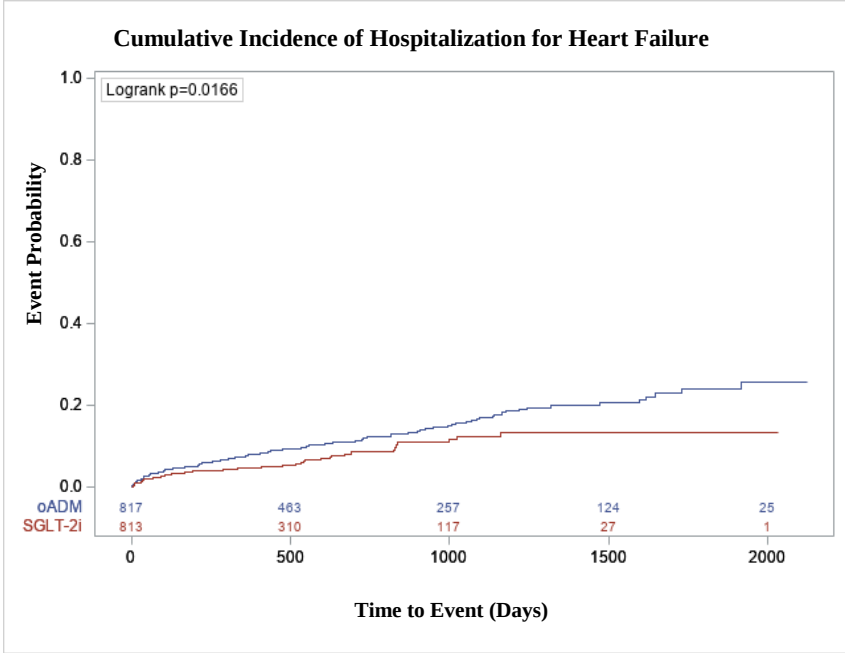
*Incidence rate per 100 person-years

CI = confidence interval; CV = cardiovascular; GLP-1RA = glucagon-like peptide-1 receptor agonist; oADM = other antidiabetic medication; SGLT-2i = sodium-glucose cotransporter-2 inhibitor

For the primary composite CV endpoint, the incidence rate for patients who were newly initiated on SGLT-2is compared to oADMs was 7.0 versus 8.5 events per 100 person-years with a significantly lower cumulative risk (HR 0.69, 95% CI: 0.52-0.92; p=0.01). Figure 3.3.1.1 shows the comparison of primary CV outcome event curves for SGLT-2is compared to oADMs.

Figure 3.3.1.1 Composite cardiovascular outcome and hospitalization for heart failure event curves for patients newly initiated on sodium-glucose cotransporter-2 inhibitors versus other antidiabetic medications



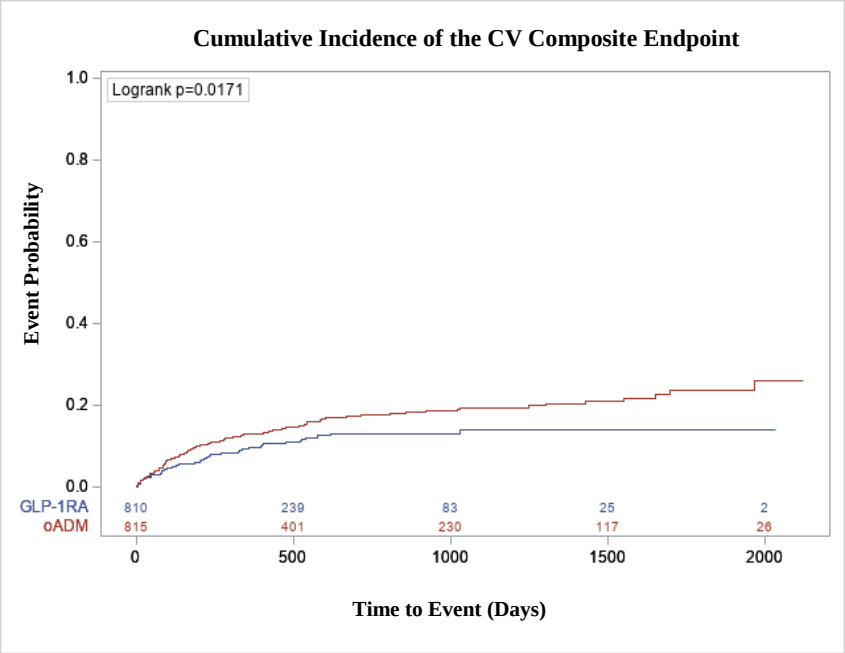


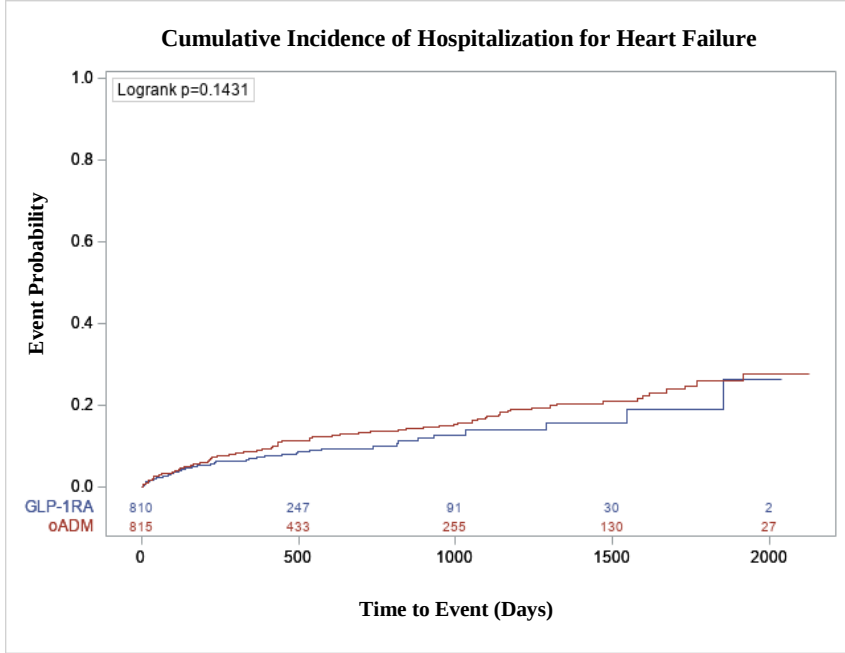
CV = cardiovascular; oADM = other antidiabetic medication; SGLT-2i = sodium-glucose cotransporter-2 inhibitor

Mean follow-up time for the composite CV endpoint for SGLT-2is versus oADMs was 473 and 683 days, respectively. Separation in event curves occurred early and was significant (log-rank test p=0.01). For hospitalization for heart failure the incidence rate for patients who initiated SGLT-2is compared to oADMs was 4.7 versus 6.3 events per person-years with a significantly lower cumulative risk (HR 0.66, 95% CI: 0.47-0.93; p=0.02). Mean follow-up time for hospitalization for heart failure for SGLT-2is versus oADMs was 490 and 750 days, respectively. Separation in event curves occurred early and was significant (log-rank test p=0.02).

When comparing patients who were newly initiated on GLP-1RAs compared to oADMs, the incidence rate for the primary composite CV endpoint was 7.6 versus 8.2 events per 100 person-years with a significantly lower cumulative risk of HR 0.69, 95% CI: 0.52-0.92; p=0.01). Figure 3.3.1.2 shows the comparison of primary CV outcome event curves for GLP-1RAs compared to oADMs.

Figure 3.3.1.2 Composite cardiovascular outcome and hospitalization for heart failure event curves for patients newly initiated on glucagon-like peptide-1 receptor agonists versus other antidiabetic medications



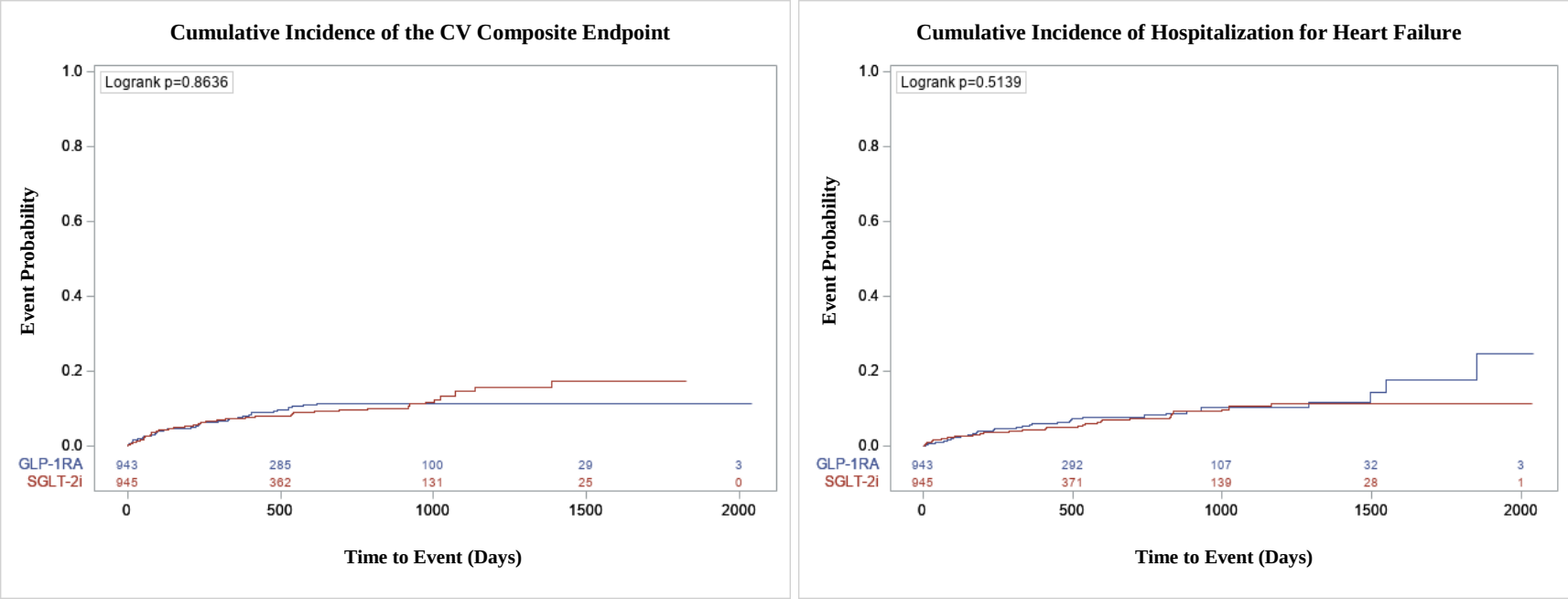


CV = cardiovascular; GLP-1RA = glucagon-like peptide-1 receptor agonist; oADM = other antidiabetic medication

Mean follow-up time for the composite CV endpoint for GLP-1RAs versus oADMs was 413 and 681 days, respectively. Separation in event curves occurred early and was significant (log-rank test p=0.02). For hospitalization for heart failure, the incidence rate for patients who initiated GLP-1RAs compared to oADMs was 6.4 versus 6.9 events per person-years with no significant difference in cumulative risk HR 0.66, 95% CI: 0.47-0.93; p=0.02). Mean follow-up time for hospitalization for heart failure for GLP-1RAs versus oADMs was 428 and 730 days, respectively. There were no significant differences in event curves (log-rank test p=0.14).

When comparing patients who were newly imitated on SGLT-2is compared to GLP-1RAs, there were no significant differences in the primary CV outcomes. For the primary composite CV endpoint, the incidence rate for patients who initiated SGLT-2is compared to SGLT-2is was 6.2 versus 6.2 events per 100 person-years with no significant difference in cumulative risk (HR 1.03, 95% CI: 0.72-1.43; p=0.86). Figure 3.3.1.3 shows the comparison of primary CV outcome event curves for SGLT-2s compared to GLP-1RAs.

Figure 3.3.1.3 Composite cardiovascular outcome and hospitalization for heart failure event curves for patients newly initiated on sodium-glucose cotransporter-2 inhibitors versus glucagon-like peptide-1 receptor agonists



CV = cardiovascular; GLP-1RA = glucagon-like peptide-1 receptor agonist; SGLT-2i = sodium-glucose cotransporter-2 inhibitor

Mean follow-up time for the composite CV endpoint for SGLT-2is versus GLP-1RAs was 481 and 420 days, respectively. There were no significant differences in event curves (log-rank test p=0.86). For hospitalizations for heart failure, the incidence rate for patients who initiated SGLT-2is compared to GLP-1RAs was 4.1 versus 4.9 events per person-years with no significant difference in cumulative risk (HR 0.88, 95% CI: (0.60-1.29); p=0.51). Mean follow-up time for the composite CV endpoint for SGLT-2is versus GLP-1RAs was 497 and 433 days, respectively. There were no significant differences in event curves (log-rank test p=0.51).

3.3.2 Secondary Cardiovascular Outcomes

Table 3.3.2.1 shows the associated risks for the secondary cardiovascular outcomes, unstable angina requiring hospitalization, stroke, MI, and coronary revascularization for patients in each pairwise propensity score matched cohort.

Table 3.3.2.1 Risk of secondary cardiovascular outcomes for patients in each pairwise propensity score matched cohort

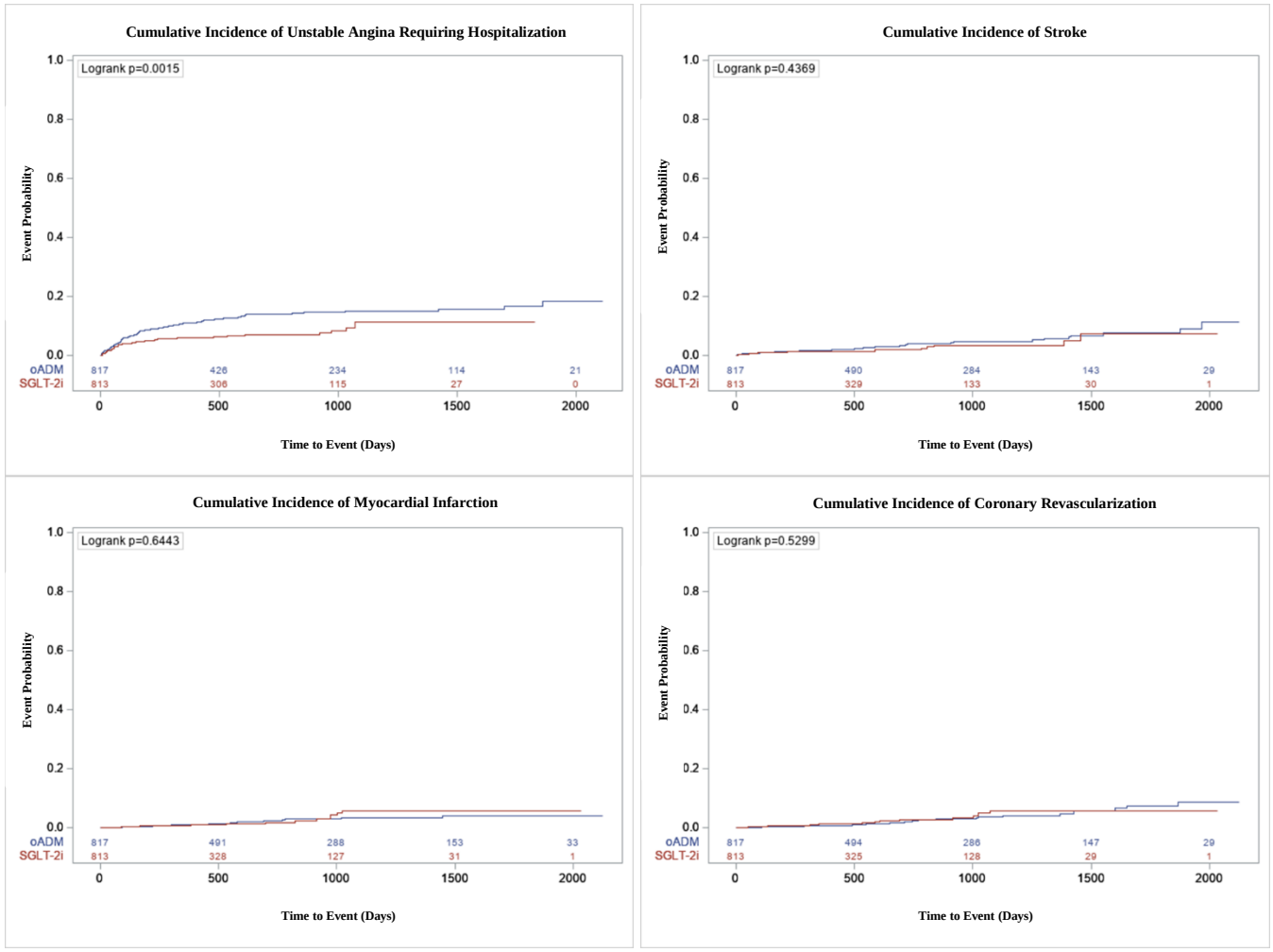
	Cohort 1 (n=818 pairs)			**Cohort 2 (n=815 pairs)**			**Cohort 3 (n=947 pairs)**		
CV Outcomes	**SGLT-2i**	**oADM**	p-value	**GLP-1RA**	**oADM**	p-value	**SGLT-2i**	**GLP-1RA**	p-value
Unstable angina requiring hospitalization									
Follow-up, years	1080	1572		938	1559		1270	1106	
Incidence rate*	4.7	6.4		5.3	6.4		4.3	4.4	
Hazard Ratio (95% CI)	0.58 (0.41-0.82)		0.002	0.59 (0.42-0.83)		0.003	1.01 (0.69-1.49)		0.96
Myocardial infarction									
Follow-up, years	1159	1834		1015	1802		1347	1179	
Incidence rate*	1.2	1.0		1.7	1.5		1.3	1.4	
Hazard Ratio (95% CI)	1.18 (0.58-2.4)		0.64	0.98 (0.53-1.82)		0.95	1.01 (0.52-1.99)		0.97
Stroke									
Follow-up, years	1162	1808		1014	1794		1353	1177	
Incidence rate*	1.5	1.8		1.2	1.2		1.1	0.8	
Hazard Ratio (95% CI)	0.79 (0.43-1.44)		0.44	0.90 (0.44-1.85)		0.78	1.43 (0.62-3.26)		0.40
Coronary revascularization									
Follow-up, years	1146	1823		1010	1803		1335	1177	
Incidence rate*	1.4	1.3		1.5	1.2		1.3	1.3	
Hazard Ratio (95% CI)	1.23 (0.64-2.37)		0.53	1.36 (0.69-2.67)		0.37	1.02 (0.52-2.03)		0.95

*Incidence rate per 100 person-years

CI = confidence interval; CV = cardiovascular; GLP-1RA = glucagon-like peptide-1 receptor agonist; oADM = other antidiabetic medication; SGLT-2i = sodium-glucose cotransporter-2 inhibitors

When comparing patients newly initiated on SGLT-2is compared to oADMs, the incidence rate for unstable angina requiring hospitalization was 4.7 versus 6.4 events per 100 person-years with a significantly lower cumulative risk (HR 0.58, 95% CI: 0.41-0.82; p=0.002). Figure 3.3.2.1 shows the comparison of secondary cardiovascular outcome event curves for SGLT-2is compared to oADMs.

Figure 3.3.2.1 Secondary cardiovascular outcomes event curves for patients newly initiated on sodium-glucose cotransporter-2 inhibitors versus other antidiabetic medications

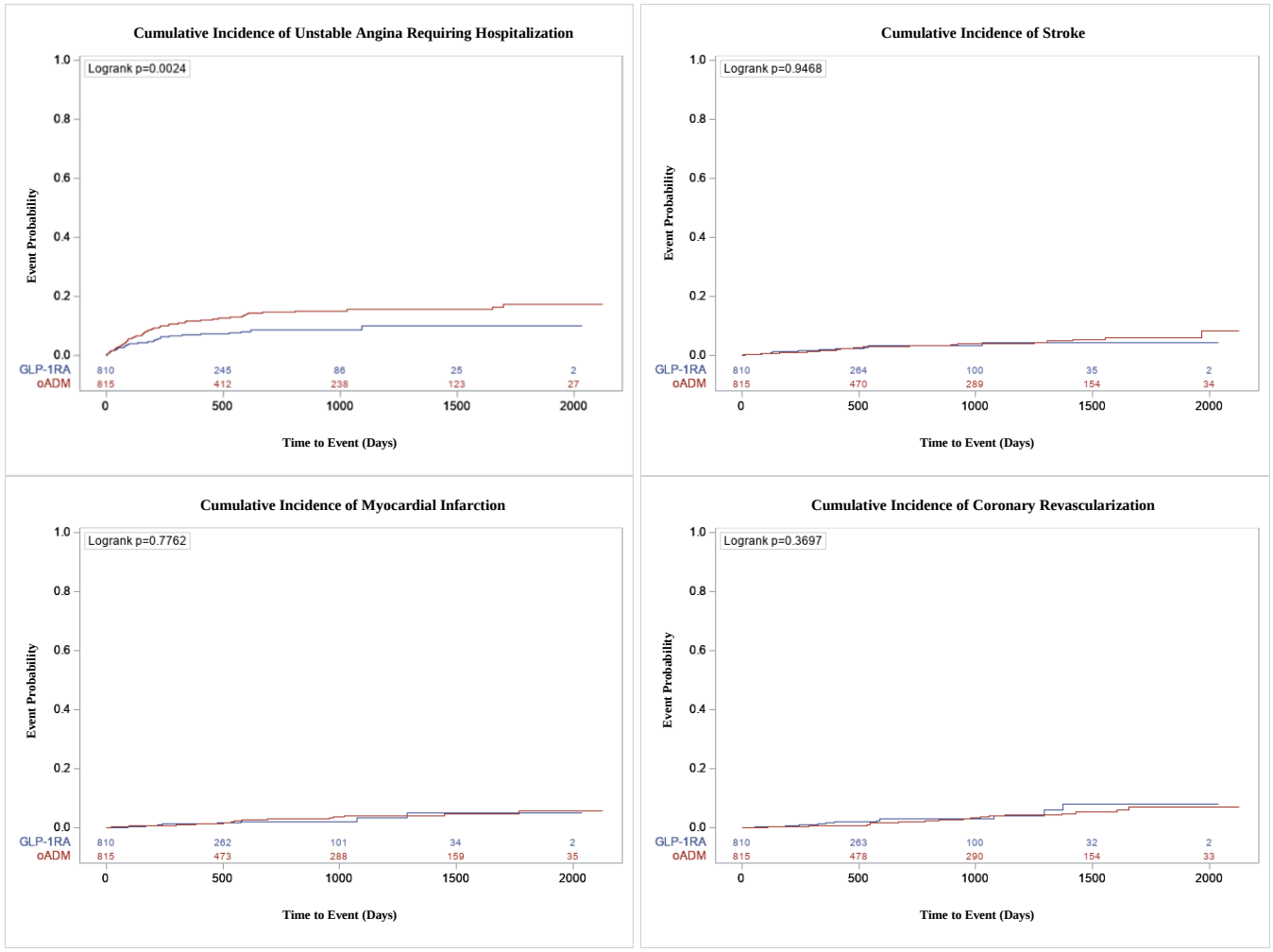


CV = cardiovascular; GLP-1RA = glucagon-like peptide-1 receptor agonist; oADM = other antidiabetic medication; SGLT-2i = sodium-glucose cotransporter-2 inhibitor

Mean follow-up time for unstable angina requiring hospitalization for SGLT-2is versus oADMs was 483 and 703 days, respectively. Separation in event curves occurred early and was significant (log-rank test p=0.002). For all other secondary outcomes, there were no significant differences between SGLT-2is versus oADMs.

When comparing patients newly initiated on GLP-1RAs compared to oADMs, the incidence rate for unstable angina requiring hospitalization was 5.3 versus 6.4 events per 100 person-years with a significantly lower cumulative risk (HR 0.58, 95% CI: 0.42-0.83; p=0.003). Figure 3.3.2.2 shows the comparison of secondary cardiovascular outcome event curves for GLP-1RAs compared to oADMs.

Figure 3.3.2.2 Secondary cardiovascular outcomes event curves for patients newly initiated on glucagon-like peptide-1 receptor agonists versus other antidiabetic medications

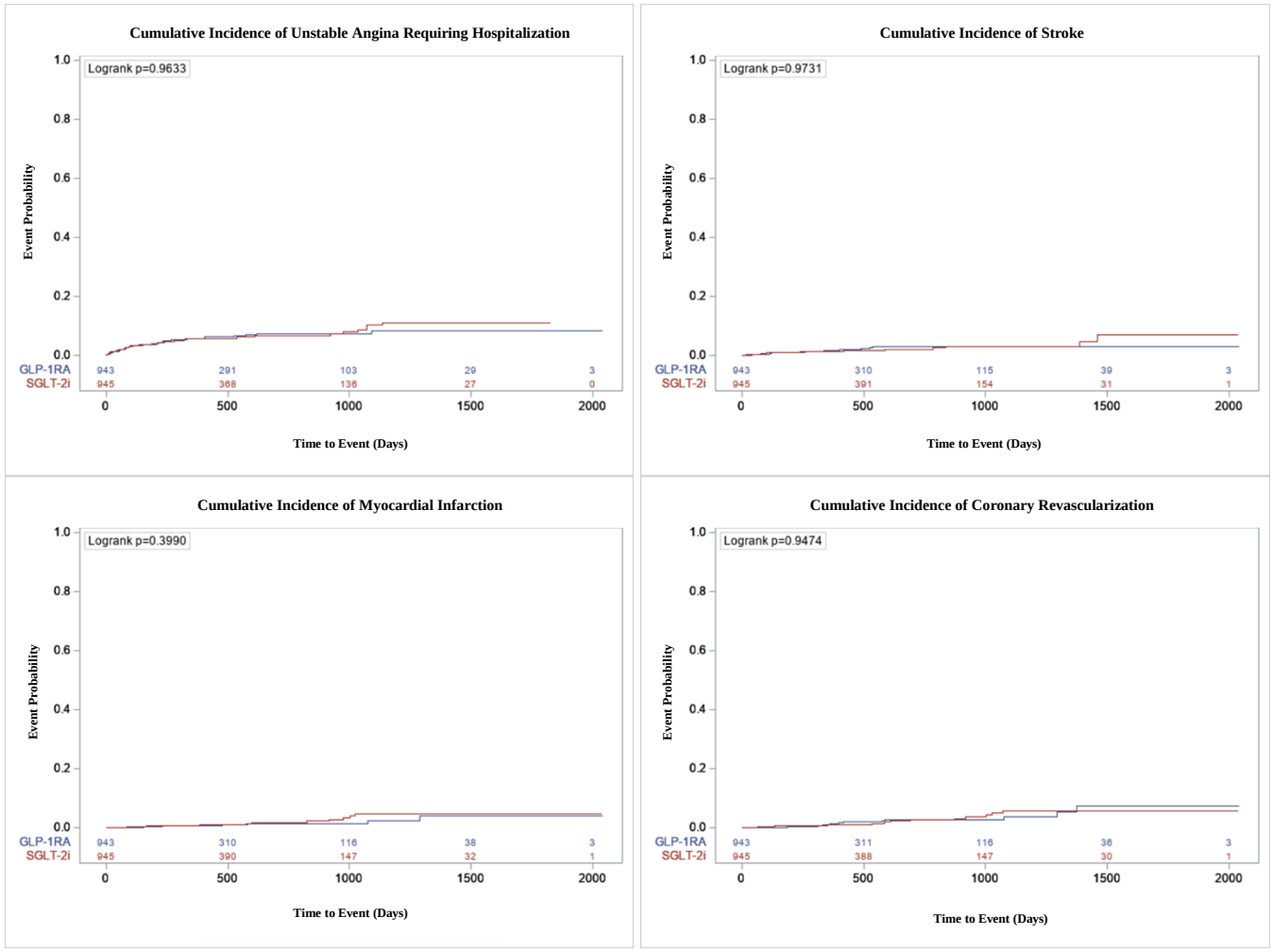


CV = cardiovascular; GLP-1RA = glucagon-like peptide-1 receptor agonist; oADM = other antidiabetic medication; SGLT-2i = sodium-glucose cotransporter-2 inhibitor

Mean follow-up time for unstable angina requiring hospitalization for GLP-1RAs versus oADMs was 420 and 699 days, respectively. Separation in event curves occurred early and was significant (log-rank test p=0.002). For all other secondary outcomes, there were no significant differences between SGLT-2is versus oADMs.

When comparing patients newly initiated on SGLT-2is compared to GLP-1RAs , the incidence rate for unstable angina requiring hospitalization For the unstable angina requiring hospitalization, the incidence rate for patients initiating GLP-1RAs compared to oADMs was 5.3 versus 6.4 events per 100 person-years with a significantly lower cumulative risk (HR 0.58, 95% CI: 0.42-0.83; p=0.003). Figure 3.3.2.3 shows the comparison of secondary cardiovascular outcome event curves for GLP-1RAs compared to oADMs.

Figure 3.3.2.3 Secondary cardiovascular outcomes event curves for patients newly initiated on sodium-glucose cotransporter-2 inhibitors versus glucagon-like peptide-1 receptor agonists



CV = cardiovascular; GLP-1RA = glucagon-like peptide-1 receptor agonist; oADM = other antidiabetic medication; SGLT-2i = sodium-glucose cotransporter-2 inhibitor

Mean follow-up time for unstable angina requiring hospitalization for GLP-1RAs versus oADMs was 420 and 699 days, respectively. Separation in event curves occurred early and was significant (log-rank test p=0.002). For all other secondary outcomes, there were no significant differences between SGLT-2is versus oADMs.

3.4 SUMMARY OF RESULTS

Objectives and Alternate Hypotheses (H_1)	Result
Objective 1 Describe and determine whether baseline demographics differ between T2D patients newly initiated on SGLT-2is versus oADMs, GLP-1RAs versus oADMs, and SGLT-2is versus GLP-1RAs.	
$H_1$1.1: The difference in age between patients newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$1.2: The difference in age between patients newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$1.3: The difference in age between patients newly initiated on SGLT2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$1.4: The difference in gender between patients newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$1.5: The difference in gender between patients newly initiated on GLP-1RAs versus oADMs is statistically significant.	Rejected
$H_1$1.6: The difference in gender between patients newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
$H_1$1.7: The difference in the proportion of patients of white race between patients newly initiated on SGLT-2is versus oADMs is statistically significant.	Rejected
$H_1$1.8: The difference in the proportion of patients of white race between patients newly initiated on GLP-1RAs versus oADMs is statistically significant.	Rejected

Objectives and Alternate Hypotheses (H_1)	Result
$H_1$1.9: The difference in the proportion of patients of white race between patients newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
$H_1$1.10: The difference in the proportion of patients of other race between patients newly initiated on SGLT-2is versus oADMs is statistically significant.	Rejected
$H_1$1.11: The difference in the proportion of patients of other race between patients newly initiated on GLP-1RAs versus oADMs is statistically significant.	Rejected
$H_1$1.12: The difference in the proportion of patients of other race between patients newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
$H_1$1.13: The difference in the proportion of patients of unknown race between patients newly initiated on SGLT-2is versus oADMs is statistically significant.	Rejected
$H_1$1.14: The difference in the proportion of patients of unknown race between patients newly initiated on GLP-1RAs versus oADMs is statistically significant.	Rejected
$H_1$1.15: The difference in the proportion of patients of unknown race between patients newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
Objective 2 Describe and determine whether baseline prevalence of comorbidities differ between T2D patients newly initiated on SGLT-2is versus oADMs, GLP-1RAs versus oADMs, SGLT-2is versus GLP-1RAs.	
$H_1$2.1: The difference in CCI scores between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Rejected
$H_1$2.2: The difference in CCI scores between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject

Objectives and Alternate Hypotheses (H_1)	Result
$H_1$2.3: The difference in CCI scores between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
$H_1$2.4: The difference in the proportion of patients with a history of CVD between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$2.5: The difference in the proportion of patients with a history of CVD between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$2.6: The difference in the proportion of patients with a history of CVD between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$2.7: The difference in the proportion of patients with a history of MI between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$2.8: The difference in the proportion of patients with a history of MI between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$2.9: The difference in the proportion of patients with a history of MI between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$2.10: The difference in the proportion of patients with a history of stroke between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$2.11: The difference in the proportion of patients with a history of stroke between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$2.12: The difference in the proportion of patients with a history of stroke between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$2.13: The difference in the proportion of patients with a history of TIA between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Rejected

Objectives and Alternate Hypotheses (H_1)	Result
$H_1$2.14: The difference in the proportion of patients with a history of TIA between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Rejected
$H_1$2.15: The difference in the proportion of patients with a history of TIA between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$2.16: The difference in the proportion of patients with unstable angina between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$2.17: The difference in the proportion of patients with unstable angina between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$2.18: The difference in the proportion of patients with unstable angina between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$2.19: The difference in the proportion of patients with angina pectoris between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$2.20: The difference in the proportion of patients with angina pectoris between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$2.21: The difference in the proportion of patients with angina pectoris between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$2.22: The difference in the proportion of patients with heart failure between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$2.23: The difference in the proportion of patients with heart failure between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject

Objectives and Alternate Hypotheses (H_1)	Result
$H_1$2.24: The difference in the proportion of patients with heart failure between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$2.25: The difference in the proportion of patients with PAD between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$2.26: The difference in the proportion of patients with PAD between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Rejected
$H_1$2.27: The difference in the proportion of patients with PAD between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$2.28: The difference in the proportion of patients with atrial fibrillation between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$2.29: The difference in the proportion of patients with atrial fibrillation between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$2.30: The difference in the proportion of patients with atrial fibrillation between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$2.31: The difference in the proportion of patients with hypertension between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Rejected
$H_1$2.32: The difference in the proportion of patients with hypertension between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$2.33: The difference in the proportion of patients with hypertension between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected

Objectives and Alternate Hypotheses (H_1)	Result
$H_1$2.34: The difference in the proportion of patients with CKD between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$2.35: The difference in the proportion of patients with CKD between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Rejected
$H_1$2.36: The difference in the proportion of patients with CKD between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
$H_1$2.37: The difference in the proportion of patients with microvascular disease between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$2.38: The difference in the proportion of patients with microvascular disease between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$2.39: The difference in the proportion of patients with microvascular disease between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$2.40: The difference in the proportion of patients with dyslipidemia between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$2.41: The difference in the proportion of patients with dyslipidemia between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$2.42: The difference in the proportion of patients with dyslipidemia between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
$H_1$2.43: The difference in the proportion of patients with obesity between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject

Objectives and Alternate Hypotheses (H_1)	Result
$H_1$2.44: The difference in the proportion of patients with obesity between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$2.45: The difference in the proportion of patients with obesity between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
Objective 3 Describe and determine whether baseline medication use differ between T2D patients newly initiated on SGLT-2is versus oADMs, GLP-1RAs versus oADMs, SGLT-2is versus GLP-1RAs.	
$H_1$3.1: The difference in the number of antidiabetic medications used between patients newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$3.2: The difference in the number of antidiabetic medications used between patients newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$3.3: The difference in the number of antidiabetic medications used between patients newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
$H_1$3.4: The difference in the proportion of patients taking metformin between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$3.5: The difference in the proportion of patients taking metformin between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$3.6: The difference in the proportion of patients taking metformin between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
$H_1$3.7: The difference in the proportion of patients taking DPP-4is between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject

Objectives and Alternate Hypotheses (H_1)	Result
$H_1$3.8: The difference in the proportion of patients taking DPP-4is between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$3.9: The difference in the proportion of patients taking DPP-4is between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
$H_1$3.10: The difference in the proportion of patients taking sulfonylureas between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$3.11: The difference in the proportion of patients taking sulfonylureas between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$3.12: The difference in the proportion of patients taking sulfonylureas between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
$H_1$3.13: The difference in the proportion of patients taking TZDs between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$3.14: The difference in the proportion of patients taking TZDs between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$3.15: The difference in the proportion of patients taking TZDs between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
$H_1$3.16: The difference in the proportion of patients taking meglinitides between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$3.17: The difference in the proportion of patients taking meglinitides between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject

Objectives and Alternate Hypotheses (H_1)	Result
$H_1$3.18: The difference in the proportion of patients taking meglinitides between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$3.19: The difference in the proportion of patients taking insulin between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$3.20: The difference in the proportion of patients taking insulin between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$3.21: The difference in the proportion of patients taking insulin between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
$H_1$3.22: The difference in the proportion of patients taking ACEis, between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$3.23: The difference in the proportion of patients taking ACEis, between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$3.24: The difference in the proportion of patients taking ACEis, between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$3.25: The difference in the proportion of patients taking ARBs between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$3.26: The difference in the proportion of patients taking ARBs between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$3.27: The difference in the proportion of patients taking ARBs between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected

Objectives and Alternate Hypotheses (H_1)	Result
$H_1$3.28: The difference in the proportion of patients taking beta blockers between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$3.29: The difference in the proportion of patients taking beta blockers between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Rejected
$H_1$3.30: The difference in the proportion of patients taking beta blockers between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$3.31: The difference in the proportion of patients taking CCBs between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Rejected
$H_1$3.32: The difference in the proportion of patients taking CCBs between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Rejected
$H_1$3.33: The difference in the proportion of patients taking CCBs between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$3.34: The difference in the proportion of patients taking thiazides between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$3.35: The difference in the proportion of patients taking thiazides between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$3.36: The difference in the proportion of patients taking thiazides between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
$H_1$3.37: The difference in the proportion of patients taking loop diuretics between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject

Objectives and Alternate Hypotheses (H_1)	Result
$H_1$3.38: The difference in the proportion of patients taking loop diuretics between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Rejected
$H_1$3.39: The difference in the proportion of patients taking loop diuretics between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
$H_1$3.40: The difference in the proportion of patients taking nitrates between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Rejected
$H_1$3.41: The difference in the proportion of patients taking nitrates between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Rejected
$H_1$3.42: The difference in the proportion of patients taking nitrates between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$3.43: The difference in the proportion of patients taking anticoagulants between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$3.44: The difference in the proportion of patients taking anticoagulants between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$3.45: The difference in the proportion of patients taking anticoagulants between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$3.46: The difference in the proportion of patients taking antiplatelets between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Rejected
$H_1$3.47: The difference in the proportion of patients taking antiplatelets between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject

Objectives and Alternate Hypotheses (H_1)	Result
$H_1$3.48: The difference in the proportion of patients taking antiplatelets between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$3.49: The difference in the proportion of patients taking statins between those who are newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$3.50: The difference in the proportion of patients taking statins between those who are newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$3.51: The difference in the proportion of patients taking statins between those who are newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
Objective 4 Describe and determine whether HbA1c prior to initiation of study medications differs between T2D patients newly initiated on SGLT-2is versus oADMs, GLP-1RAs versus oADMs, SGLT-2is versus GLP-1RAs.	
$H_1$4.1: The difference in proportion of patients missing HbA1c values newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$4.2: The difference in proportion of patients missing HbA1c values newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$4.3: The difference in proportion of patients missing HbA1c values newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$4.4: The difference in HbA1c between patients newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$4.5: The difference in HbA1c between patients newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$4.6: The difference in HbA1c between patients newly initiated SGLT-2is versus GLP-1RAs is statistically significant.	Failed to reject
Objective 5	

Objectives and Alternate Hypotheses (H_1)	Result
Determine whether the cumulative incidence or hazard of CV outcomes differ between T2D patients newly initiated on SGLT-2is versus oADMs, GLP-1RAs versus oADMs, SGLT-2is versus GLP-1RAs.	
$H_1$5.1: The difference in the cumulative incidence or hazard of the composite CV endpoint between patients newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$5.2: The difference in the cumulative incidence or hazard of the composite CV endpoint between patients newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$5.3: The difference in the cumulative incidence or hazard of the composite CV endpoint between patients newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$5.4 The difference in the cumulative incidence or hazard of hospitalizations for heart failure between patients newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$5.5: The difference in the cumulative incidence or hazard of hospitalizations for heart failure between patients newly initiated on GLP-1RAs versus oADMs is statistically significant.	Rejected
$H_1$5.6: The difference in the cumulative incidence or hazard of hospitalizations for heart failure between patients newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected
$H_1$5.7: The difference in the cumulative incidence or hazard of MI between patients newly initiated on SGLT-2is versus oADMs is statistically significant.	Rejected
$H_1$5.8: The difference in the cumulative incidence or hazard of MI between patients newly initiated on GLP-1RAs versus oADMs is statistically significant.	Rejected
$H_1$5.9: The difference in the cumulative incidence or hazard of MI between patients newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected

Objectives and Alternate Hypotheses (H_1)	Result
$H_1$5.10: The difference in the cumulative incidence or hazard of unstable angina requiring hospitalization between patients newly initiated on SGLT-2is versus oADMs is statistically significant.	Failed to reject
$H_1$5.11: The difference in the cumulative incidence or hazard of unstable angina requiring hospitalization between patients newly initiated on GLP-1RAs versus oADMs is statistically significant.	Failed to reject
$H_1$5.12: The difference in the cumulative incidence or hazard of unstable angina requiring hospitalization between patients newly initiated on SGLT-2is versus GLP-1RAs is statistically significant.	Rejected

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCB = Calcium channel blocker; CCBs = calcium-channel blocker; CCI = Charlson Comorbidity Index; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DPP-4i = dipeptidyl peptidase-4 inhibitor; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = hemoglobin A1c; oADM = other antidiabetic medication; MI = myocardial infarction; PAD = peripheral artery disease; SGLT-2i = sodium-glucose cotransporter-2 inhibitor; TIA = transient ischemic attack; TZD = thiazolidinediones

Chapter 4: Discussion and Conclusion

4.1 DISCUSSION

This is the first population-based real-world study to evaluate the differences in patient characteristics and the comparative effectiveness of initiating SGLT-2is, GLP-1RAs, or oADMs in regards to CV outcomes in an integrated delivery network setting. In our institution, T2D patients who were initiated on SGLT-2is and GLP-1RAs were relatively similar. Patients initiating GLP-1RAs had higher prevalence of CKD and obesity at baseline, which is likely as a result of the contraindications and precautions of use in patients with renal impairment associated with SGLT-2is and the preference of GLP-1RAs over SGLT-2is for minimizing weight gain or promoting weight loss. In addition, differences in baseline antidiabetic use were observed between these groups with SGLT-2i patients had higher utilization of other oral agents. One reasonable explanation may be due to patients being switch to SGLT-2is due to the relatively easier oral to oral conversion in therapy, whereas the conversion from an oral agent to an injectable such as a GLP-1RA may not be preferred by most patients. Insulin use was higher for patients initiated on GLP-1RAs compared to SGLT-2is, likely explained as a result of the increasing popularity of combining both agents for their synergistic effects on glucose-lowering and opposing weight effects. This is the basis of the development of GLP-1RA and insulin combination products.

In contrast, patients who were initiated on SGLT-2is and GLP-1RAs compared to oADMs showed significant differences in baseline characteristic. These patients tended to be younger with a lower prevalence of CVD but did have higher prevalence of microvascular disease. This is surprising since based on our estimate of diabetes severity based on multiple proxy indicators, it would seem that most of our patients who were newly initiated on oADMs had low severity and may have been more recently diagnosed with T2D, given that over 50% of our oADM group were new initiators of metformin, had less antidiabetic medications at baseline, and had lower HbA1c values. However, it is important to note that almost 50% of our patients had missing HbA1c values.

Nevertheless, our method of propensity score matching each pairwise comparison group allowed us to evenly distribute measured covariates between each group.

Our findings showed that both SGLT-2is and GLP-1RAs significantly reduced the risk of the composite CV endpoint comprised of MI, stroke, unstable angina, and coronary revascularization compared to oADMs by 31% and 30%, respectively, in a population of patients with T2D who had a low prevalence of established CVD. The majority of CVOTs that have been completed to date recruited a high CV risk population with almost all patients having established CVD in order to accumulate enough events to allow for a meaningful estimate of the risk, which is not representative of the general T2D population.

While it is difficult to compare our results with most of the CVOTs for these agents due to the lack of access to mortality data, we can at least compare some of the data regarding nonfatal events. Our study showed that SGLT-2is reduced the risk of heart failure hospitalization by 34%, which is in line with what was seen for empagliflozin in EMPA-REG OUTCOME, canagliflozin in CANVAS, and dapagliflozin in DECLARE-TIMI 58 at 35%, 33%, and 27%, respectively.[37–39] However, almost all of the patients that were included in those trials either had established CVD, with the exception of DECLARE-TIMI 58 which also included patients with only CV risk factors, while the majority (greater than 80%) of the patients in our study did not have any history of CVD with less than 9% having a history of heart failure. This provides more evidence in support of considering these agents early in the treatment decision algorithm for primary prevention of CVD, specifically for heart failure. For GLP-1RAs, our results showed a non-significant reduction in heart failure hospitalization compared to oADMs, which is also consistent in what is seen in the GLP-1RA CVOTs. When comparing the reduction of MACE risk of both agents compared to placebo in CVOTs, the Kaplan-Meier curves were seen to separate early within the first few months for SGLT-2i agents, whereas the curves start to separate after about 12 months.[50] This may suggest that CV benefit for SGLT-2is are primarily driven by reductions in heart failure hospitalizations mediated by their positive hemodynamic effects, while CV benefits for GLP-

1RAs are primarily as a result of their effect on altering the progression of atherosclerosis, which is a relatively longer process than the hemodynamic effects that are seen with SGLT-2is. Consequently, a longer follow-up period, which was not attainable in our study, may have been needed to see these favorable effects in reducing ASCVD risk for GLP-1RAs, as well as for SGLT-2is. Interestingly, both agents demonstrated significant reductions in unstable angina requiring hospitalizations, which was not observed in clinical trials.

The lack of differences in CV outcomes between SGLT-2is and GLP-1As in our study provides some evidence that both drug classes, in general, may be equally effective in reducing CV risk in the broad T2D population. Currently, clinical guidelines only provide recommendations for these drug classes to be used specifically for T2D patients with established CVD. Moreover, only select agents within each drug class are currently recommended, which is limited to empagliflozin, canagliflozin, and liraglutide. However, it seems that a new paradigm shift in primary prevention of CVD may be underway. In March 2019, the American College of Cardiology (ACC) and the American Heart Association (AHA) released the 2019 Primary Prevention in Cardiovascular Disease guidelines, which outlines strategies focused on the primary prevention of CVD.[51] Included in the guideline is a recommendation on primary prevention of CVD in adults with T2D as well as a treatment algorithm, recommending the initiation of either an SGLT-2i or a GLP-1RA as second-line or adjunct treatment to lifestyle modifications and metformin, although it was given a weak (level IIb) recommendation. Nonetheless, these new guidelines do not single out any preferred agent within each class, but rather provides the recommendation across their entirety. More evidence surrounding the broader use of these agents is expected to emerge in the upcoming years with investigations on the use of SGLT-2is in the absence of T2D, CVOT results that include a population of patients without CVD, as is the case with REWIND (dulaglutide) where only 31% reportedly had established CVD, as well as the first oral GLP-1RA (semaglutide) to come to market.

4.2 LIMITATIONS

There were several limitations in this study. First, given the observational and retrospective nature of the study design, there is always a risk of residual unmeasured confounding that could not be entirely accounted for from the information available with the limited bandwidth of single-system administrative claims and EHR data alone. Out of 9,477 unique patients in the study, only 45.7% (4,328) had available HbA1c, which prevented the ability to use HbA1c as a covariate in our propensity score models. Multiple imputation and missing indicator methods were considered a possible solution[52]; however, it was unlikely the best approach without introducing significant bias within our results, given that over 50% of the study population had missing values. Second, we were unable to directly consider the duration of diabetes for each patient, which has been found to be positively correlated with an increased risk of CV outcomes.[53] Nonetheless, we were able to incorporate other related measures as proxies for evaluating diabetes severity, such as the presence of micro- and macrovascular disease and the number of baseline antidiabetic agents. Third, our data source did not allow us to investigate CV death as a study endpoint of interest, which prevents the ability to compare our results to other studies that examined CV mortality. However, because we included other CV outcomes that were assessed in other studies, we were able to compare our results for individual CV endpoints. Finally, our results should be taken in the context of the population sample that was included, which was limited to an insured adult T2D population in Texas. Therefore, our results may not be generalizable outside of our institution or geographic coverage. However, despite these limitations, our results were generally consistent with results from other studies and provides useful insights that can be applied to similar institutions to help guide health-care decision making.

4.3 CONCLUSIONS

Both SGLT-2is and GLP-1RAs showed significant reductions in the composite CV outcome and unstable angina requiring hospitalization compared to other antidiabetic drug classes.

However, only SGLT-2is were associated with a lower risk of HF hospitalizations. This suggests that both SGLT-2is and GLP-1RAs are both equally effective at reducing CVD outcomes in patients with T2D compared to other antidiabetic agents. However, SGLT-2is may be more effective for heart failure-related events. Nevertheless, CV outcomes were similar between SGLT-2is and GLP-1RAs when compared to each other. This study provides real-world evidence for patients, payers, and providers to consider the selection of these novel antidiabetic agents with demonstrated CV benefits over other agents regardless of CVD status. Future investigation is needed regarding whether heart failure benefit with SGLT-2is is similar between heart failure patients with reduced ejection fraction and preserved ejection fraction. In addition, investigation surrounding use of both drug classes in the absence of T2D for CVD risk reduction may be warranted.

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Appendix A: Search Terms for Antidiabetic Drug Classes

Drug Class	Search Terms	
Sodium-glucose cotransporter-2 inhibitors		
	CANAGLIFLOZIN	JARDIANCE
	DAPAGLIFLOZIN	QTERN
	EMPAGLIFLOZIN	SEGLUROMET
	ERTUGLIFLOZIN	STEGLATRO
	FARXIGA	STEGLUJAN
	GLYXAMBI	SYNJARDY
	INVOKAMET	XIGDUO
	INVOKANA	
Glucagon-like peptide-1 receptor agonists		
	ADLYXIN	OZEMPIC
	ALBIGLUTIDE	SEMAGLUTIDE
	BYDUREON	SOLIQUA
	BYETTA	TANZEUM
	DULAGLUTIDE	TRULICITY
	EXENATIDE	VICTOZA
	LIRAGLUTIDE	XULTOPHY
	LIXISENATIDE	
Other antidiabetic medications		
Metformin	ACTOPLUS	JENTADUETO
	AVANDAMET	KAZANO
	FORTAMET	KOMBIGLYZE
	GLUCOPHAGE	METFORMIN
	GLUCOPHAGE XR	PRANDIMET
	GLUCOVANCE	SEGLUROMET
	GLUMETZA	SYNJARDY
	INVOKAMET	XIGDUO
	JANUMET	
Dipeptidyl peptidase-4 inhibitors	ALOGLIPTIN	NESINA
	GLYXAMBI	ONGLYZA
	JANUMET	OSENI
	JANUVIA	QTERN
	JENTADUETO	SAXAGLIPTIN
	JUVISYNC	SITAGLIPTIN
	KAZANO	STEGLUJAN
	KOMBIGLYZE	TRADJENTA
	LINAGLIPTIN	

Sulfonylureas	AMARYL	GLUCOTROL
	CHLORPROPAMIDE	GLYBURIDE
	DIABETA	GLYNASE
	GLIMEPIRIDE	TOLAZAMIDE
	GLIPIZIDE	TOLBUTAMIDE
Thiazolidinediones	ACTOPLUS	AVANDIA
	ACTOS	PIOGLITAZONE
	AVANDAMET	ROSIGLITAZONE
	AVANDARYL	
Alpha-glucosidase inhibitors	ACARBOSE	PRECOSE
	MIGLITOL	
Meglinitides	NATEGLINIDE	REPAGLINIDE
	PRANDIMET	STARLIX
	PRANDIN	
Insulin	ADMELOG	LANTUS
	AFREZZA	LEVEMIR
	APIDRA	NOVOLIN
	BASAGLAR	NOVOLOG
	FIASP	SOLIQUA
	HUMALOG	TOUJEO
	HUMULIN	TRESIBA
	INSULIN	XULTOPHY

Appendix B. Diagnosis Codes for Cardiovascular Outcomes

Myocardial infarction definition: Hospital discharge/inpatient diagnosis of relevant codes					
Code Type	**Code**	**Code Type**	**Code**	**Code Type**	**Code**
ICD9 DIAGNOSIS	410	ICD9 DIAGNOSIS	410.61	ICD10 DIAGNOSIS	I21.3
ICD9 DIAGNOSIS	410	ICD9 DIAGNOSIS	410.7	ICD10 DIAGNOSIS	I21.4
ICD9 DIAGNOSIS	410	ICD9 DIAGNOSIS	410.7	ICD10 DIAGNOSIS	I21.9
ICD9 DIAGNOSIS	410.01	ICD9 DIAGNOSIS	410.71	ICD10 DIAGNOSIS	I21.A
ICD9 DIAGNOSIS	410.1	ICD9 DIAGNOSIS	410.8	ICD10 DIAGNOSIS	I21.A1
ICD9 DIAGNOSIS	410.1	ICD9 DIAGNOSIS	410.8	ICD10 DIAGNOSIS	I21.A9
ICD9 DIAGNOSIS	410.11	ICD9 DIAGNOSIS	410.81	ICD10 DIAGNOSIS	I22
ICD9 DIAGNOSIS	410.2	ICD9 DIAGNOSIS	410.9	ICD10 DIAGNOSIS	I22.0
ICD9 DIAGNOSIS	410.2	ICD9 DIAGNOSIS	410.9	ICD10 DIAGNOSIS	I22.1
ICD9 DIAGNOSIS	410.21	ICD9 DIAGNOSIS	410.91	ICD10 DIAGNOSIS	I22.2
ICD9 DIAGNOSIS	410.3	ICD10 DIAGNOSIS	I21	ICD10 DIAGNOSIS	I22.8
ICD9 DIAGNOSIS	410.3	ICD10 DIAGNOSIS	I21.0	ICD10 DIAGNOSIS	I22.9
ICD9 DIAGNOSIS	410.31	ICD10 DIAGNOSIS	I21.01	ICD10 DIAGNOSIS	I23.0
ICD9 DIAGNOSIS	410.4	ICD10 DIAGNOSIS	I21.02	ICD10 DIAGNOSIS	I23.1
ICD9 DIAGNOSIS	410.4	ICD10 DIAGNOSIS	I21.09	ICD10 DIAGNOSIS	I23.2
ICD9 DIAGNOSIS	410.41	ICD10 DIAGNOSIS	I21.1	ICD10 DIAGNOSIS	I23.3
ICD9 DIAGNOSIS	410.5	ICD10 DIAGNOSIS	I21.11	ICD10 DIAGNOSIS	I23.4
ICD9 DIAGNOSIS	410.5	ICD10 DIAGNOSIS	I21.19	ICD10 DIAGNOSIS	I23.5
ICD9 DIAGNOSIS	410.51	ICD10 DIAGNOSIS	I21.2	ICD10 DIAGNOSIS	I23.6
ICD9 DIAGNOSIS	410.6	ICD10 DIAGNOSIS	I21.21	ICD10 DIAGNOSIS	I23.8
ICD9 DIAGNOSIS	410.6	ICD10 DIAGNOSIS	I21.29		
Unstable angina definition: Hospital discharge/inpatient diagnosis of relevant codes:					
Code Type	**Code**	**Code Type**	**Code**	**Code Type**	**Code**
ICD9 DIAGNOSIS	411	ICD10 DIAGNOSIS	I24	ICD10 DIAGNOSIS	I25.710
ICD9 DIAGNOSIS	411	ICD10 DIAGNOSIS	I24.0	ICD10 DIAGNOSIS	I25.720
ICD9 DIAGNOSIS	411.1	ICD10 DIAGNOSIS	I24.1	ICD10 DIAGNOSIS	I25.730
ICD9 DIAGNOSIS	411.8	ICD10 DIAGNOSIS	I24.8	ICD10 DIAGNOSIS	I25.750
ICD9 DIAGNOSIS	411.81	ICD10 DIAGNOSIS	I24.9	ICD10 DIAGNOSIS	I25.760
ICD9 DIAGNOSIS	411.89	ICD10 DIAGNOSIS	I25.110	ICD10 DIAGNOSIS	I25.790
ICD10 DIAGNOSIS	I20.0	ICD10 DIAGNOSIS	I25.700		
Ischemic stroke definition: Hospital discharge/inpatient diagnosis of relevant codes					
Code Type	**Code**	**Code Type**	**Code**	**Code Type**	**Code**
ICD9 DIAGNOSIS	433.01	ICD10 DIAGNOSIS	I63.19	ICD10 DIAGNOSIS	I63.421
ICD9 DIAGNOSIS	433.11	ICD10 DIAGNOSIS	I63.2	ICD10 DIAGNOSIS	I63.422
ICD9 DIAGNOSIS	433.21	ICD10 DIAGNOSIS	I63.20	ICD10 DIAGNOSIS	I63.423
ICD9 DIAGNOSIS	433.31	ICD10 DIAGNOSIS	I63.21	ICD10 DIAGNOSIS	I63.429
ICD9 DIAGNOSIS	433.81	ICD10 DIAGNOSIS	I63.211	ICD10 DIAGNOSIS	I63.43

ICD9 DIAGNOSIS	433.91	ICD10 DIAGNOSIS	I63.212	ICD10 DIAGNOSIS	I63.431
ICD9 DIAGNOSIS	434.01	ICD10 DIAGNOSIS	I63.213	ICD10 DIAGNOSIS	I63.432
ICD9 DIAGNOSIS	434.11	ICD10 DIAGNOSIS	I63.219	ICD10 DIAGNOSIS	I63.433
ICD9 DIAGNOSIS	434.91	ICD10 DIAGNOSIS	I63.22	ICD10 DIAGNOSIS	I63.439
ICD9 DIAGNOSIS	436	ICD10 DIAGNOSIS	I63.23	ICD10 DIAGNOSIS	I63.44
ICD10 DIAGNOSIS	G43.6	ICD10 DIAGNOSIS	I63.231	ICD10 DIAGNOSIS	I63.441
ICD10 DIAGNOSIS	G43.601	ICD10 DIAGNOSIS	I63.232	ICD10 DIAGNOSIS	I63.442
ICD10 DIAGNOSIS	G43.609	ICD10 DIAGNOSIS	I63.233	ICD10 DIAGNOSIS	I63.443
ICD10 DIAGNOSIS	G43.611	ICD10 DIAGNOSIS	I63.239	ICD10 DIAGNOSIS	I63.449
ICD10 DIAGNOSIS	G43.619	ICD10 DIAGNOSIS	I63.29	ICD10 DIAGNOSIS	I63.49
ICD10 DIAGNOSIS	G46.3	ICD10 DIAGNOSIS	I63.3	ICD10 DIAGNOSIS	I63.5
ICD10 DIAGNOSIS	G46.4	ICD10 DIAGNOSIS	I63.30	ICD10 DIAGNOSIS	I63.50
ICD10 DIAGNOSIS	G95.11	ICD10 DIAGNOSIS	I63.31	ICD10 DIAGNOSIS	I63.51
ICD10 DIAGNOSIS	I63	ICD10 DIAGNOSIS	I63.311	ICD10 DIAGNOSIS	I63.511
ICD10 DIAGNOSIS	I63.0	ICD10 DIAGNOSIS	I63.312	ICD10 DIAGNOSIS	I63.512
ICD10 DIAGNOSIS	I63.00	ICD10 DIAGNOSIS	I63.313	ICD10 DIAGNOSIS	I63.513
ICD10 DIAGNOSIS	I63.01	ICD10 DIAGNOSIS	I63.319	ICD10 DIAGNOSIS	I63.519
ICD10 DIAGNOSIS	I63.011	ICD10 DIAGNOSIS	I63.32	ICD10 DIAGNOSIS	I63.52
ICD10 DIAGNOSIS	I63.012	ICD10 DIAGNOSIS	I63.321	ICD10 DIAGNOSIS	I63.521
ICD10 DIAGNOSIS	I63.013	ICD10 DIAGNOSIS	I63.322	ICD10 DIAGNOSIS	I63.522
ICD10 DIAGNOSIS	I63.019	ICD10 DIAGNOSIS	I63.323	ICD10 DIAGNOSIS	I63.523
ICD10 DIAGNOSIS	I63.02	ICD10 DIAGNOSIS	I63.329	ICD10 DIAGNOSIS	I63.529
ICD10 DIAGNOSIS	I63.03	ICD10 DIAGNOSIS	I63.33	ICD10 DIAGNOSIS	I63.53
ICD10 DIAGNOSIS	I63.031	ICD10 DIAGNOSIS	I63.331	ICD10 DIAGNOSIS	I63.531
ICD10 DIAGNOSIS	I63.032	ICD10 DIAGNOSIS	I63.332	ICD10 DIAGNOSIS	I63.532
ICD10 DIAGNOSIS	I63.033	ICD10 DIAGNOSIS	I63.333	ICD10 DIAGNOSIS	I63.533
ICD10 DIAGNOSIS	I63.039	ICD10 DIAGNOSIS	I63.339	ICD10 DIAGNOSIS	I63.539
ICD10 DIAGNOSIS	I63.09	ICD10 DIAGNOSIS	I63.34	ICD10 DIAGNOSIS	I63.54
ICD10 DIAGNOSIS	I63.1	ICD10 DIAGNOSIS	I63.341	ICD10 DIAGNOSIS	I63.541
ICD10 DIAGNOSIS	I63.10	ICD10 DIAGNOSIS	I63.342	ICD10 DIAGNOSIS	I63.542
ICD10 DIAGNOSIS	I63.11	ICD10 DIAGNOSIS	I63.343	ICD10 DIAGNOSIS	I63.543
ICD10 DIAGNOSIS	I63.111	ICD10 DIAGNOSIS	I63.349	ICD10 DIAGNOSIS	I63.549
ICD10 DIAGNOSIS	I63.112	ICD10 DIAGNOSIS	I63.39	ICD10 DIAGNOSIS	I63.59
ICD10 DIAGNOSIS	I63.113	ICD10 DIAGNOSIS	I63.4	ICD10 DIAGNOSIS	I63.6
ICD10 DIAGNOSIS	I63.119	ICD10 DIAGNOSIS	I63.40	ICD10 DIAGNOSIS	I63.8
ICD10 DIAGNOSIS	I63.12	ICD10 DIAGNOSIS	I63.41	ICD10 DIAGNOSIS	I63.9
ICD10 DIAGNOSIS	I63.13	ICD10 DIAGNOSIS	I63.411	ICD10 DIAGNOSIS	I97.810
ICD10 DIAGNOSIS	I63.131	ICD10 DIAGNOSIS	I63.412	ICD10 DIAGNOSIS	I97.811
ICD10 DIAGNOSIS	I63.132	ICD10 DIAGNOSIS	I63.413	ICD10 DIAGNOSIS	I97.82
ICD10 DIAGNOSIS	I63.133	ICD10 DIAGNOSIS	I63.419	ICD10 DIAGNOSIS	I97.820
ICD10 DIAGNOSIS	I63.139	ICD10 DIAGNOSIS	I63.42	ICD10 DIAGNOSIS	I97.821
ICD9 DIAGNOSIS	435	ICD10 DIAGNOSIS	G45.0	ICD10 DIAGNOSIS	I67.84

ICD9 DIAGNOSIS	435	ICD10 DIAGNOSIS	G45.1	ICD10 DIAGNOSIS	I67.841
ICD9 DIAGNOSIS	435.1	ICD10 DIAGNOSIS	G45.2	ICD10 DIAGNOSIS	I67.848
ICD9 DIAGNOSIS	435.2	ICD10 DIAGNOSIS	G45.8	ICD10 DIAGNOSIS	M47.0
ICD9 DIAGNOSIS	435.3	ICD10 DIAGNOSIS	G45.9	ICD10 DIAGNOSIS	M47.02
ICD9 DIAGNOSIS	435.8	ICD10 DIAGNOSIS	G46.0	ICD10 DIAGNOSIS	M47.021
ICD9 DIAGNOSIS	435.9	ICD10 DIAGNOSIS	G46.1	ICD10 DIAGNOSIS	M47.022
ICD10 DIAGNOSIS	G45	ICD10 DIAGNOSIS	G46.2	ICD10 DIAGNOSIS	M47.029
Heart failure definition: Hospital discharge/inpatient diagnosis of relevant codes					
Code Type	Code	Code Type	Code	Code Type	Code
ICD9 DIAGNOSIS	398.91	ICD9 DIAGNOSIS	428.32	ICD10 DIAGNOSIS	I50.31
ICD9 DIAGNOSIS	402.01	ICD9 DIAGNOSIS	428.33	ICD10 DIAGNOSIS	I50.32
ICD9 DIAGNOSIS	402.11	ICD9 DIAGNOSIS	428.4	ICD10 DIAGNOSIS	I50.33
ICD9 DIAGNOSIS	402.91	ICD9 DIAGNOSIS	428.4	ICD10 DIAGNOSIS	I50.4
ICD9 DIAGNOSIS	404.01	ICD9 DIAGNOSIS	428.41	ICD10 DIAGNOSIS	I50.40
ICD9 DIAGNOSIS	404.03	ICD9 DIAGNOSIS	428.42	ICD10 DIAGNOSIS	I50.41
ICD9 DIAGNOSIS	404.11	ICD9 DIAGNOSIS	428.43	ICD10 DIAGNOSIS	I50.42
ICD9 DIAGNOSIS	404.13	ICD9 DIAGNOSIS	428.9	ICD10 DIAGNOSIS	I50.43
ICD9 DIAGNOSIS	404.91	ICD10 DIAGNOSIS	I09.81	ICD10 DIAGNOSIS	I50.8
ICD9 DIAGNOSIS	404.93	ICD10 DIAGNOSIS	I11.0	ICD10 DIAGNOSIS	I50.81
ICD9 DIAGNOSIS	428	ICD10 DIAGNOSIS	I13.0	ICD10 DIAGNOSIS	I50.810
ICD9 DIAGNOSIS	428	ICD10 DIAGNOSIS	I13.2	ICD10 DIAGNOSIS	I50.811
ICD9 DIAGNOSIS	428.1	ICD10 DIAGNOSIS	I50	ICD10 DIAGNOSIS	I50.812
ICD9 DIAGNOSIS	428.2	ICD10 DIAGNOSIS	I150.1	ICD10 DIAGNOSIS	I50.813
ICD9 DIAGNOSIS	428.2	ICD10 DIAGNOSIS	I50.2	ICD10 DIAGNOSIS	I50.814
ICD9 DIAGNOSIS	428.21	ICD10 DIAGNOSIS	I50.20	ICD10 DIAGNOSIS	I50.82
ICD9 DIAGNOSIS	428.22	ICD10 DIAGNOSIS	I50.21	ICD10 DIAGNOSIS	I50.83
ICD9 DIAGNOSIS	428.23	ICD10 DIAGNOSIS	I50.22	ICD10 DIAGNOSIS	I50.84
ICD9 DIAGNOSIS	428.3	ICD10 DIAGNOSIS	I50.23	ICD10 DIAGNOSIS	I50.89
ICD9 DIAGNOSIS	428.3	ICD10 DIAGNOSIS	I50.3	ICD10 DIAGNOSIS	I50.9
ICD9 DIAGNOSIS	428.31	ICD10 DIAGNOSIS	I50.30	ICD10 DIAGNOSIS	I97.13
Coronary Revascularization definition					
Code Type	**Code**	**Code Type**	**Code**	**Code Type**	**Code**
ICD9 PROCEDURE	36.1	ICD10 PROCEDURE	02110KF	ICD10 PROCEDURE	02124K8
ICD9 PROCEDURE	36.11	ICD10 PROCEDURE	02110KW	ICD10 PROCEDURE	02124K9
ICD9 PROCEDURE	36.12	ICD10 PROCEDURE	02110Z3	ICD10 PROCEDURE	02124KC
ICD9 PROCEDURE	36.13	ICD10 PROCEDURE	02110Z8	ICD10 PROCEDURE	02124KF
ICD9 PROCEDURE	36.14	ICD10 PROCEDURE	02110Z9	ICD10 PROCEDURE	02124KW
ICD9 PROCEDURE	36.15	ICD10 PROCEDURE	02110ZC	ICD10 PROCEDURE	02124Z3
ICD9 PROCEDURE	36.16	ICD10 PROCEDURE	02110ZF	ICD10 PROCEDURE	02124Z8
ICD9 PROCEDURE	36.17	ICD10 PROCEDURE	211344	ICD10 PROCEDURE	02124Z9
ICD9 PROCEDURE	36.19	ICD10 PROCEDURE	02113D4	ICD10 PROCEDURE	02124ZC

ICD10 PROCEDURE	210098	ICD10 PROCEDURE	211444	ICD10 PROCEDURE	02124ZF
ICD10 PROCEDURE	210099	ICD10 PROCEDURE	211493	ICD10 PROCEDURE	213
ICD10 PROCEDURE	021009C	ICD10 PROCEDURE	211498	ICD10 PROCEDURE	213093
ICD10 PROCEDURE	021009F	ICD10 PROCEDURE	211499	ICD10 PROCEDURE	213098
ICD10 PROCEDURE	021009W	ICD10 PROCEDURE	021149C	ICD10 PROCEDURE	213099
ICD10 PROCEDURE	02100A3	ICD10 PROCEDURE	021149F	ICD10 PROCEDURE	021309C
ICD10 PROCEDURE	02100A8	ICD10 PROCEDURE	021149W	ICD10 PROCEDURE	021309F
ICD10 PROCEDURE	02100A9	ICD10 PROCEDURE	02114A3	ICD10 PROCEDURE	021309W
ICD10 PROCEDURE	02100AC	ICD10 PROCEDURE	02114A8	ICD10 PROCEDURE	02130A3
ICD10 PROCEDURE	02100AF	ICD10 PROCEDURE	02114A9	ICD10 PROCEDURE	02130A8
ICD10 PROCEDURE	02100AW	ICD10 PROCEDURE	02114AC	ICD10 PROCEDURE	02130A9
ICD10 PROCEDURE	02100J3	ICD10 PROCEDURE	02114AF	ICD10 PROCEDURE	02130AC
ICD10 PROCEDURE	02100J8	ICD10 PROCEDURE	02114AW	ICD10 PROCEDURE	02130AF
ICD10 PROCEDURE	02100J9	ICD10 PROCEDURE	02114D4	ICD10 PROCEDURE	02130AW
ICD10 PROCEDURE	02100JC	ICD10 PROCEDURE	02114J3	ICD10 PROCEDURE	02130J3
ICD10 PROCEDURE	02100JF	ICD10 PROCEDURE	02114J8	ICD10 PROCEDURE	02130J8
ICD10 PROCEDURE	02100JW	ICD10 PROCEDURE	02114J9	ICD10 PROCEDURE	02130J9
ICD10 PROCEDURE	02100K3	ICD10 PROCEDURE	02114JC	ICD10 PROCEDURE	02130JC
ICD10 PROCEDURE	02100K8	ICD10 PROCEDURE	02114JF	ICD10 PROCEDURE	02130JF
ICD10 PROCEDURE	02100K9	ICD10 PROCEDURE	02114JW	ICD10 PROCEDURE	02130JW
ICD10 PROCEDURE	02100KC	ICD10 PROCEDURE	02114K3	ICD10 PROCEDURE	02130K3
ICD10 PROCEDURE	02100KF	ICD10 PROCEDURE	02114K8	ICD10 PROCEDURE	02130K8
ICD10 PROCEDURE	02100KW	ICD10 PROCEDURE	02114K9	ICD10 PROCEDURE	02130K9
ICD10 PROCEDURE	02100Z3	ICD10 PROCEDURE	02114KC	ICD10 PROCEDURE	02130KC
ICD10 PROCEDURE	02100Z8	ICD10 PROCEDURE	02114KF	ICD10 PROCEDURE	02130KF
ICD10 PROCEDURE	02100Z9	ICD10 PROCEDURE	02114KW	ICD10 PROCEDURE	02130KW
ICD10 PROCEDURE	02100ZC	ICD10 PROCEDURE	02114Z3	ICD10 PROCEDURE	02130Z3
ICD10 PROCEDURE	02100ZF	ICD10 PROCEDURE	02114Z8	ICD10 PROCEDURE	02130Z8
ICD10 PROCEDURE	210344	ICD10 PROCEDURE	02114Z9	ICD10 PROCEDURE	02130Z9
ICD10 PROCEDURE	02103D4	ICD10 PROCEDURE	02114ZC	ICD10 PROCEDURE	02130ZC
ICD10 PROCEDURE	210444	ICD10 PROCEDURE	02114ZF	ICD10 PROCEDURE	02130ZF
ICD10 PROCEDURE	210493	ICD10 PROCEDURE	212	ICD10 PROCEDURE	213344
ICD10 PROCEDURE	210498	ICD10 PROCEDURE	212093	ICD10 PROCEDURE	02133D4
ICD10 PROCEDURE	210499	ICD10 PROCEDURE	212098	ICD10 PROCEDURE	213444
ICD10 PROCEDURE	021049C	ICD10 PROCEDURE	212099	ICD10 PROCEDURE	213493
ICD10 PROCEDURE	021049F	ICD10 PROCEDURE	021209C	ICD10 PROCEDURE	213498
ICD10 PROCEDURE	021049W	ICD10 PROCEDURE	021209F	ICD10 PROCEDURE	213499
ICD10 PROCEDURE	02104A3	ICD10 PROCEDURE	021209W	ICD10 PROCEDURE	021349C
ICD10 PROCEDURE	02104A8	ICD10 PROCEDURE	02120A3	ICD10 PROCEDURE	021349F
ICD10 PROCEDURE	02104A9	ICD10 PROCEDURE	02120A8	ICD10 PROCEDURE	021349W
ICD10 PROCEDURE	02104AC	ICD10 PROCEDURE	02120A9	ICD10 PROCEDURE	02134A3
ICD10 PROCEDURE	02104AF	ICD10 PROCEDURE	02120AC	ICD10 PROCEDURE	02134A8

ICD10 PROCEDURE	02104AW	ICD10 PROCEDURE	02120AF	ICD10 PROCEDURE	02134A9
ICD10 PROCEDURE	02104D4	ICD10 PROCEDURE	02120AW	ICD10 PROCEDURE	02134AC
ICD10 PROCEDURE	02104J3	ICD10 PROCEDURE	02120J3	ICD10 PROCEDURE	02134AF
ICD10 PROCEDURE	02104J8	ICD10 PROCEDURE	02120J8	ICD10 PROCEDURE	02134AW
ICD10 PROCEDURE	02104J9	ICD10 PROCEDURE	02120J9	ICD10 PROCEDURE	02134D4
ICD10 PROCEDURE	02104JC	ICD10 PROCEDURE	02120JC	ICD10 PROCEDURE	02134J3
ICD10 PROCEDURE	02104JF	ICD10 PROCEDURE	02120JF	ICD10 PROCEDURE	02134J8
ICD10 PROCEDURE	02104JW	ICD10 PROCEDURE	02120JW	ICD10 PROCEDURE	02134J9
ICD10 PROCEDURE	02104K3	ICD10 PROCEDURE	02120K3	ICD10 PROCEDURE	02134JC
ICD10 PROCEDURE	02104K8	ICD10 PROCEDURE	02120K8	ICD10 PROCEDURE	02134JF
ICD10 PROCEDURE	02104K9	ICD10 PROCEDURE	02120K9	ICD10 PROCEDURE	02134JW
ICD10 PROCEDURE	02104KC	ICD10 PROCEDURE	02120KC	ICD10 PROCEDURE	02134K3
ICD10 PROCEDURE	02104KF	ICD10 PROCEDURE	02120KF	ICD10 PROCEDURE	02134K8
ICD10 PROCEDURE	02104KW	ICD10 PROCEDURE	02120KW	ICD10 PROCEDURE	02134K9
ICD10 PROCEDURE	02104Z3	ICD10 PROCEDURE	02120Z3	ICD10 PROCEDURE	02134KC
ICD10 PROCEDURE	02104Z8	ICD10 PROCEDURE	02120Z8	ICD10 PROCEDURE	02134KF
ICD10 PROCEDURE	02104Z9	ICD10 PROCEDURE	02120Z9	ICD10 PROCEDURE	02134KW
ICD10 PROCEDURE	02104ZC	ICD10 PROCEDURE	02120ZC	ICD10 PROCEDURE	02134Z3
ICD10 PROCEDURE	02104ZF	ICD10 PROCEDURE	02120ZF	ICD10 PROCEDURE	02134Z8
ICD10 PROCEDURE	211	ICD10 PROCEDURE	212344	ICD10 PROCEDURE	02134Z9
ICD10 PROCEDURE	211093	ICD10 PROCEDURE	02123D4	ICD10 PROCEDURE	02134ZC
ICD10 PROCEDURE	211098	ICD10 PROCEDURE	212444	ICD10 PROCEDURE	02134ZF
ICD10 PROCEDURE	211099	ICD10 PROCEDURE	212493	CPT4	33510
ICD10 PROCEDURE	021109C	ICD10 PROCEDURE	212498	CPT4	33511
ICD10 PROCEDURE	021109F	ICD10 PROCEDURE	212499	CPT4	33512
ICD10 PROCEDURE	021109W	ICD10 PROCEDURE	021249C	CPT4	33513
ICD10 PROCEDURE	02110A3	ICD10 PROCEDURE	021249F	CPT4	33514
ICD10 PROCEDURE	02110A8	ICD10 PROCEDURE	021249W	CPT4	33516
ICD10 PROCEDURE	02110A9	ICD10 PROCEDURE	02124A3	CPT4	33517
ICD10 PROCEDURE	02110AC	ICD10 PROCEDURE	02124A8	CPT4	33518
ICD10 PROCEDURE	02110AF	ICD10 PROCEDURE	02124A9	CPT4	33519
ICD10 PROCEDURE	02110AW	ICD10 PROCEDURE	02124AC	CPT4	33521
ICD10 PROCEDURE	02110J3	ICD10 PROCEDURE	02124AF	CPT4	33522
ICD10 PROCEDURE	02110J8	ICD10 PROCEDURE	02124AW	CPT4	33523
ICD10 PROCEDURE	02110J9	ICD10 PROCEDURE	02124D4	CPT4	33530
ICD10 PROCEDURE	02110JC	ICD10 PROCEDURE	02124J3	CPT4	33533
ICD10 PROCEDURE	02110JF	ICD10 PROCEDURE	02124J8	CPT4	33534
ICD10 PROCEDURE	02110JW	ICD10 PROCEDURE	02124J9	CPT4	33535
ICD10 PROCEDURE	02110K3	ICD10 PROCEDURE	02124JC	CPT4	33536
ICD10 PROCEDURE	02110K8	ICD10 PROCEDURE	02124JF	CPT4	33572
ICD10 PROCEDURE	02110K9	ICD10 PROCEDURE	02124JW	CPT4	4110F
ICD10 PROCEDURE	02110KC	ICD10 PROCEDURE	02124K3		

ICD9 PROCEDURE	0.66	ICD10 PROCEDURE	02713ZZ	ICD10 PROCEDURE	02733ZZ
ICD9 PROCEDURE	36	ICD10 PROCEDURE	271446	ICD10 PROCEDURE	273446
ICD9 PROCEDURE	36	ICD10 PROCEDURE	027144Z	ICD10 PROCEDURE	027344Z
ICD9 PROCEDURE	36.01	ICD10 PROCEDURE	02714D6	ICD10 PROCEDURE	02734D6
ICD9 PROCEDURE	36.02	ICD10 PROCEDURE	02714DZ	ICD10 PROCEDURE	02734DZ
ICD9 PROCEDURE	36.05	ICD10 PROCEDURE	02714T6	ICD10 PROCEDURE	02734T6
ICD9 PROCEDURE	36.06	ICD10 PROCEDURE	02714TZ	ICD10 PROCEDURE	02734TZ
ICD9 PROCEDURE	36.07	ICD10 PROCEDURE	02714Z6	ICD10 PROCEDURE	02734Z6
ICD9 PROCEDURE	36.09	ICD10 PROCEDURE	02714ZZ	ICD10 PROCEDURE	02734ZZ
ICD10 PROCEDURE	270	ICD10 PROCEDURE	272	ICD10 PROCEDURE	02C00ZZ
ICD10 PROCEDURE	270046	ICD10 PROCEDURE	272046	ICD10 PROCEDURE	02C03ZZ
ICD10 PROCEDURE	027004Z	ICD10 PROCEDURE	027204Z	ICD10 PROCEDURE	02C04ZZ
ICD10 PROCEDURE	02700D6	ICD10 PROCEDURE	02720D6	ICD10 PROCEDURE	02C10ZZ
ICD10 PROCEDURE	02700DZ	ICD10 PROCEDURE	02720DZ	ICD10 PROCEDURE	02C13ZZ
ICD10 PROCEDURE	02700T6	ICD10 PROCEDURE	02720T6	ICD10 PROCEDURE	02C14ZZ
ICD10 PROCEDURE	02700TZ	ICD10 PROCEDURE	02720TZ	ICD10 PROCEDURE	02C20ZZ
ICD10 PROCEDURE	02700Z6	ICD10 PROCEDURE	02720Z6	ICD10 PROCEDURE	02C23ZZ
ICD10 PROCEDURE	02700ZZ	ICD10 PROCEDURE	02720ZZ	ICD10 PROCEDURE	02C24ZZ
ICD10 PROCEDURE	270346	ICD10 PROCEDURE	272346	ICD10 PROCEDURE	02C30ZZ
ICD10 PROCEDURE	027034Z	ICD10 PROCEDURE	027234Z	ICD10 PROCEDURE	02C33ZZ
ICD10 PROCEDURE	02703D6	ICD10 PROCEDURE	02723D6	ICD10 PROCEDURE	02C34ZZ
ICD10 PROCEDURE	02703DZ	ICD10 PROCEDURE	02723DZ	ICD10 PROCEDURE	02Q03ZZ
ICD10 PROCEDURE	02703T6	ICD10 PROCEDURE	02723T6	ICD10 PROCEDURE	02Q04ZZ
ICD10 PROCEDURE	02703TZ	ICD10 PROCEDURE	02723TZ	ICD10 PROCEDURE	02Q13ZZ
ICD10 PROCEDURE	02703Z6	ICD10 PROCEDURE	02723Z6	ICD10 PROCEDURE	02Q14ZZ
ICD10 PROCEDURE	02703ZZ	ICD10 PROCEDURE	02723ZZ	ICD10 PROCEDURE	02Q23ZZ
ICD10 PROCEDURE	270446	ICD10 PROCEDURE	272446	ICD10 PROCEDURE	02Q24ZZ
ICD10 PROCEDURE	027044Z	ICD10 PROCEDURE	027244Z	ICD10 PROCEDURE	02Q33ZZ
ICD10 PROCEDURE	02704D6	ICD10 PROCEDURE	02724D6	ICD10 PROCEDURE	02Q34ZZ
ICD10 PROCEDURE	02704DZ	ICD10 PROCEDURE	02724DZ	ICD10 PROCEDURE	X2C0361
ICD10 PROCEDURE	02704T6	ICD10 PROCEDURE	02724T6	ICD10 PROCEDURE	X2C1361
ICD10 PROCEDURE	02704TZ	ICD10 PROCEDURE	02724TZ	ICD10 PROCEDURE	X2C2361
ICD10 PROCEDURE	02704Z6	ICD10 PROCEDURE	02724Z6	ICD10 PROCEDURE	X2C3361
ICD10 PROCEDURE	02704ZZ	ICD10 PROCEDURE	02724ZZ	CPT4	92920
ICD10 PROCEDURE	271	ICD10 PROCEDURE	273	CPT4	92928
ICD10 PROCEDURE	271046	ICD10 PROCEDURE	273046	CPT4	92929
ICD10 PROCEDURE	027104Z	ICD10 PROCEDURE	027304Z	CPT4	92933
ICD10 PROCEDURE	02710D6	ICD10 PROCEDURE	02730D6	CPT4	92934
ICD10 PROCEDURE	02710DZ	ICD10 PROCEDURE	02730DZ	CPT4	92937
ICD10 PROCEDURE	02710T6	ICD10 PROCEDURE	02730T6	CPT4	92938
ICD10 PROCEDURE	02710TZ	ICD10 PROCEDURE	02730TZ	CPT4	92941
ICD10 PROCEDURE	02710Z6	ICD10 PROCEDURE	02730Z6	CPT4	92943

ICD10 PROCEDURE	02710ZZ	ICD10 PROCEDURE	02730ZZ	CPT4	92944
ICD10 PROCEDURE	271346	ICD10 PROCEDURE	273346	CPT4	92973
ICD10 PROCEDURE	027134Z	ICD10 PROCEDURE	027334Z	CPT4	92980
ICD10 PROCEDURE	02713D6	ICD10 PROCEDURE	02733D6	CPT4	92981
ICD10 PROCEDURE	02713DZ	ICD10 PROCEDURE	02733DZ	CPT4	92982
ICD10 PROCEDURE	02713T6	ICD10 PROCEDURE	02733T6	CPT4	92984
ICD10 PROCEDURE	02713TZ	ICD10 PROCEDURE	02733TZ	CPT4	92995
ICD10 PROCEDURE	02713Z6	ICD10 PROCEDURE	02733Z6	CPT4	92996